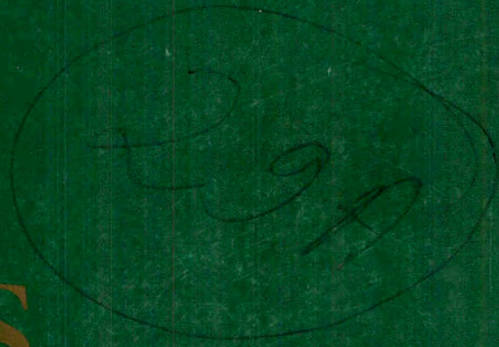


uk-HO (759-4-PO24757

Volume 11, Number 3, May 1991
Shawall 1411

ANNALS
of Saudi Medicine



ACT FAST WITH ACTILYSE



Actilyse
alteplase
tissue plasminogen activator

In acute MI time is critical. Heart attack victims need emergency facilities and treatment without delay. Now, many hospitals across the country are using new therapies to treat heart attacks – therapies that must be given as early as possible in the course of an attack to minimize heart muscle damage.

Early thrombolytic treatment with Actilyse dissolves clots in blocked coronary arteries resulting in rapid and effective reperfusion of ischaemic myocardium¹. Clinically this results in improvement in LV function², reduction in infarct size³, fewer cardiac complications⁴ and, above all, reduction in mortality⁵.

Actilyse is nature's own protein, without allergic or antigenic potential⁶ that does not react with antistreptococcal antibodies. In the emergency room infusion related hypotension is minimised and the short half life and fibrin specificity make Actilyse treatment compatible with other invasive interventions like angioplasty or emergency CABG.

Consider Actilyse. Nature's own life-saving thrombolytic that opens arteries fast. Because in acute MI, every minute counts.

References

1. TIMI Study Group N Engl J Med 1985; 312 (13) 932
2. Guerci AD N Engl J Med 1987; 317: 1613-1618
3. Aust. Nat. Study Lancet 1988; 1: 203-207
4. O'Rourke M Circulation 1988; 77: (6) 1311-1315
5. Van de Werf J AM Coll Cardiol 1988; 12: 14A-9A
6. de Bono DP Pharm Jour 1985; 54-55



**Boehringer
Ingelheim**



P.O. Box 463, Jeddah 21411
Kingdom of Saudi Arabia

Vol. 11
Volume 11, Number 3, May 1991
Shawwal 1411

ANNALS of Saudi Medicine

EDITORIAL BOARD

PETER B. HERDSON, MB, ChB, PhD, FRCPA, FRACR, EDITOR-IN-CHIEF

MOHAMMED AKHTAR, MD, FCAP

MAGID AMER, MD, FRCS(E), FRCP(C), FACP

CARLOS G. DURAN, MD, PhD

SALAH R. AL-FAQIH, MB, ChB, FRCS (GLASG), FRCS (ENGLAND)

NADIR FARID, MBBC, FRCP (LONDON), FRCP(C), FACP

M. ZUHEIR AL-KAWI, MD, FAAN

ABDUL AZIZ AL-MESHARI, FRCOG

MANSOUR AL-NOZHA, MB, BS, FRCP(LOND), FRCPI

KHALID F. TABBARA, MD

SAADI TAHER, FRCP

EDITORS

PETER B. HERDSON, MB, ChB, PhD, FRCPA, FRACR,
Editor-In-Chief

SAADI TAHER, FRCP, Administrative Editor

M. ZUHEIR AL-KAWI, MD, FAAN, Arabic Text Editor

BETTY P. NOTZON, Senior Editor

MARY ANNE DE SANTIS, Assistant Editor

EDITORIAL ASSISTANTS

VIRGINIA J. CROSIAR

SHIRLEY M. MOFFITT

The *Annals of Saudi Medicine* is published bimonthly and is a joint project of the King Saud University College of Medicine and King Khalid University Hospital, P.O. Box 2925, Riyadh 11461, Saudi Arabia, and King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. It is typeset and printed at the King Saud University Press. The *Annals* is distributed and Arabic abstracts are prepared, in association with Dr. Zuheir Al-Kawi, by staff of the Office Services Department of the King Faisal Specialist Hospital and Research Centre. All correspondence, reprint, and subscription information requests should be addressed to the Publications Office. Subscription price SR25 per issue.

Publications Office
Annals of Saudi Medicine
King Faisal Specialist Hospital and Research Centre
P.O. Box 3354
Riyadh 11211, Saudi Arabia

Advertising Representative:
PRC Associates
Pathtrace House
91-99 High Street, Banstead
Surrey SM7 2NL
Telephone: (0737)-373544
Fax: (0737)-362813

All articles published represent the opinions of the authors and do not reflect official policy of the *Annals*. All rights are reserved to the *Annals of Saudi Medicine*. No part of the journal may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or via any storage or retrieval system, without written permission from the journal.

Indexed by Current Contents, Excerpta Medica,
and Current Awareness in Biological Sciences.
ISSN 0256-4947

ANNALS OF SAUDI MEDICINE

Aims and Scope

The *Annals of Saudi Medicine* is a joint project of the King Faisal Specialist Hospital and Research Centre and the King Saud University College of Medicine and King Khalid University Hospital. The journal is typeset and printed at the King Saud University Press, Riyadh, Saudi Arabia. Since July 1985, the *Annals* has incorporated *The King Faisal Specialist Hospital Medical Journal*, established in 1980.

The *Annals* is a bimonthly multidisciplinary medical journal. High-quality papers, written in English, dealing with aspects of clinical, academic or investigative medicine or research will be welcome. Emphasis is placed on matters relating to medicine in Saudi Arabia in particular, and the Middle East in general, though articles are welcome from anywhere in the world, and the *Annals* has worldwide readership.

The *Annals* publishes original articles, case reports, letters to the editor, editorials, and from time to time, special communications, commentaries, and review articles. Abstracts of meetings and symposia sponsored by the Joint Board for Postgraduate Medical Education of Saudi Arabia are published, and the proceedings of such symposia may be published if the Editorial Board considers them appropriate and relevant. The Editorial Board wishes to minimize delay between manuscript submission, decision, and publication, and accordingly authors are requested to follow carefully the instructions set out under "Information for Authors."



King Saud University Press – A.H. 1411

ADVISORY BOARD

J. P. Blandy, MA, DM, MCh, FRCS, FACS
The London Hospital and St. Peter's Hospital
London, England, UK

Robert M. Blizzard, MD
Professor of Pediatrics
Director, Children's Medical Center
University of Virginia School of Medicine
Charlottesville, Virginia, USA

G. J. Ebrahim, FRCP(E), FRCP(GLASG)
Reader in Tropical Child Health
Institute of Child Health
University of London
London, England, UK

**Alan E. H. Emery, MD, PhD, DSc, FRCP(E),
MFCM, FRCS(E)**
Emeritus Professor of Human Genetics
University of Edinburgh
Edinburgh, Scotland, UK

Gilbert H. Fletcher, MD
Professor of Radiotherapy
Division of Radiotherapy
The University of Texas System Cancer Center
M.D. Anderson Hospital and Tumor Institute
Houston, Texas, USA

Richard J. Glasscock, MD
Professor and Chairman
Department of Medicine
Harbor-UCLA Medical Center
UCLA School of Medicine
Torrance, California, USA

Richard L. Goode, MD
Professor of Surgery
Division of Otolaryngology and
Head and Neck Surgery
Stanford Medical Center
Stanford, California, USA

Bertron M. Groves, MD
Associate Professor of Medicine
Director, Cardiac Catheterization Laboratory
University of Colorado Health Sciences Center
Denver, Colorado, USA

John Bernard Henry, MD
President
State University of New York Health
Science Center at Syracuse
Syracuse, New York, USA

Howard W. Jones, III, MD
Director of Gynecologic Oncology
Professor of Obstetrics and Gynecology
Vanderbilt University
Nashville, Tennessee, USA

David N. S. Kerr, MB, ChB, MSc, FRCP, FRCP(E)
Dean, Royal Postgraduate Medical School
Hammersmith Hospital
London, England, UK

Ronald D. Miller, MD
Professor and Chairman of Anesthesia
Professor of Pharmacology
University of California, San Francisco
San Francisco, California, USA

J. P. Mohr, MD
Sciarr Professor of Clinical Neurology
Neurological Institute
College of Physicians & Surgeons of Columbia University
New York, New York, USA

William L. Nyhan, MD, PhD
Professor and Chairman
Department of Pediatrics
School of Medicine
University of California, San Diego
La Jolla, California, USA

Roy M. Pitkin, MD
Professor and Chairman
Department of Obstetrics and Gynecology
UCLA School of Medicine
Los Angeles, California, USA

P. P. Rickham, MD, MS, FRCS, FRACS, DCH
Professor, Department of Pediatric Surgery
Universitätskinderklinik
Zurich, Switzerland

Fred S. Rosen, MD

James L. Gamble Professor of Pediatrics
(Harvard Medical School)
The Children's Hospital
Boston, Massachusetts, USA

Robert W. Schrier, MD

Professor and Chairman
Department of Medicine
Head, Division of Renal Diseases
University of Colorado School of Medicine
Denver, Colorado, USA

Norman E. Shumway, MD, PhD

Frances and Charles D. Field Professor and
Chairman, Department of Cardiovascular Surgery
Stanford University School of Medicine
Stanford, California, USA

Harlan J. Spjut, MD

Fulbright Professor of Pathology
Department of Pathology
Baylor College of Medicine
Houston, Texas, USA

**Miltiadis A. Stefadouros, MD, FACP, FACC,
FCCP, FACA, FAHA**

Professor of Medicine (Cardiology)
Chairman, Department of Medicine
King Fahad Hospital
Saudi Arabian National Guard
Riyadh, Saudi Arabia

A. J. Strong, MA, FRCS(E)

Consultant Neurosurgeon
The Neurosurgical Unit
Guy's, Maudsley and
King's College Hospitals
De Crespigny Park
London, England, UK

William B. Strong, MD

Charbonnier Professor of Pediatrics
Chief, Section of Pediatric Cardiology
Medical College of Georgia
Augusta, Georgia, USA

P. K. Thomas, DSc, MD, FRCP

Professor of Neurology
Institute of Neurology
Royal Free Hospital School of Medicine
University of London
London, England, UK

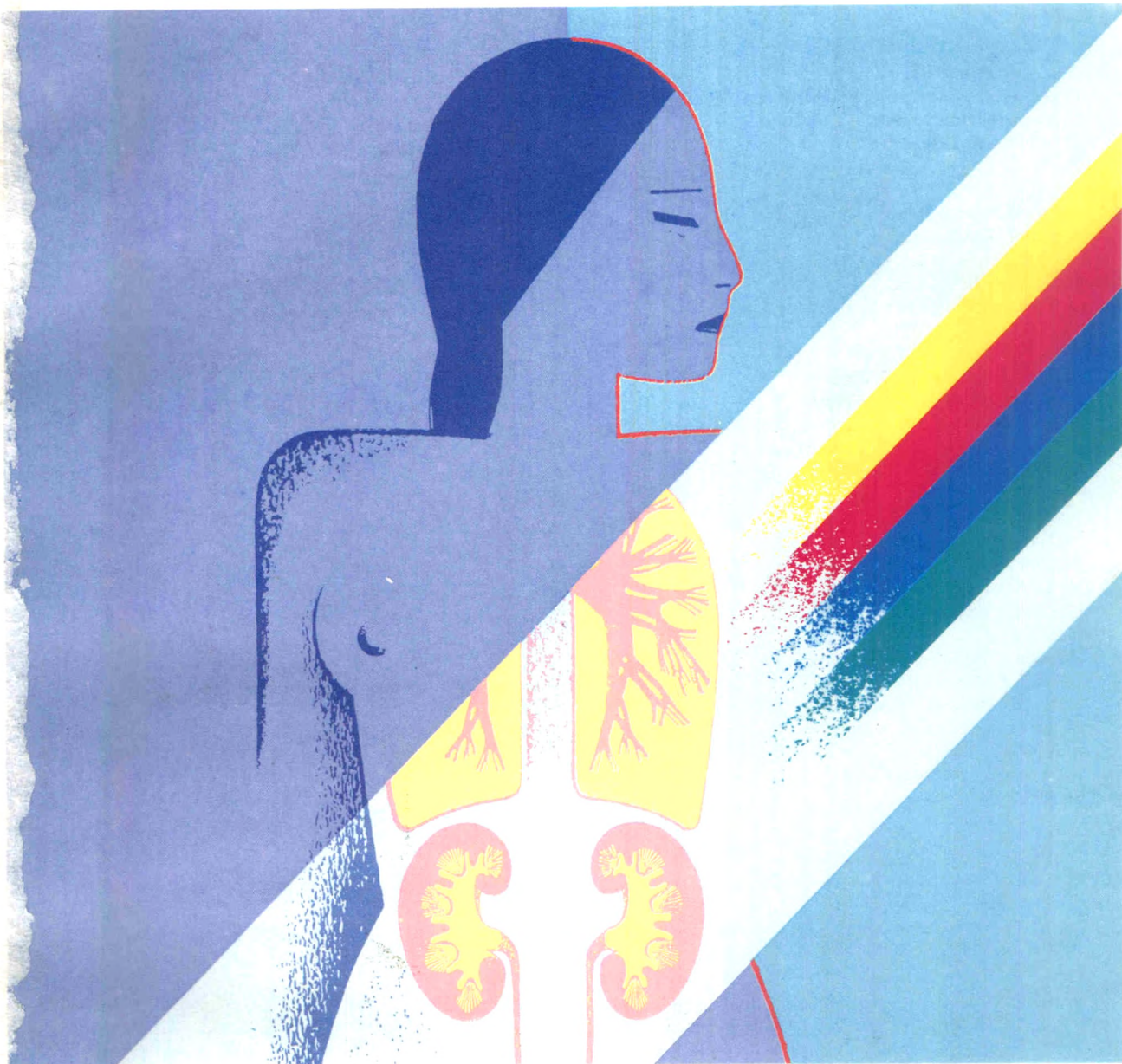
John A. Washington, II, MD

Chairman, Department of Microbiology
The Cleveland Clinic Foundation
Cleveland, Ohio, USA

**Graham H. Whitehouse, MB,BS, FRCP,
FRCR, DMRD, AKC**

Professor of Diagnostic Radiology
University of Liverpool
Liverpool, England, UK

Antibiotic management of bacterial infections



Creating a new confidence

Ciprobay[®]
Ciprofloxacin

Ciprobay: Ciprofloxacin (as HCl · H₂O): tablets 250, 500, 750 mg; (as lactate): infusion fluids (50 ml, 100 ml) 100 mg/200 mg; infusion fluid concentrate (10 ml) 100 mg. **Packs:** Country specific.

Indications: Infections (due to sensitive organisms) of the respiratory tract, middle ear, sinuses, eyes, kidneys and urinary tract, genital organs (including gonorrhoea), abdomen (gastrointestinal tract, biliary tract, peritonitis), skin and soft tissues, bones and joints; further, septicæmia, infections in patients with reduced host defence, and for selective gut decontamination.

Dosage: Depending on indication, 125–750 mg (oral) b.i.d. or 100–200 mg (i.v.) b.i.d. Acute gonorrhoea a single dose of 250 mg (oral) or 100 mg (i.v.). Reduce dose if creatinine clearance below 20 ml/min. See full prescribing information.

Contraindications: Hypersensitivity to ciprofloxacin or other quinolones. Children, juveniles, pregnancy and lactation.

Precautions: Elderly patients, epileptics and patients with CNS damage.

Interactions: Oral: mineral-containing antacids reduce absorption of ciprofloxacin. Oral/i.v.: Ciprofloxacin can increase theophylline serum concentration. Concomitant intake with NSAIDs can provoke convulsions. Transient rise of serum creatinine was observed when administered simultaneously with cyclosporin.

Side effects: GI, CNS, hypersensitivity, musculoskeletal, cardiovascular and other reactions; effects on blood and laboratory parameters. See full prescribing information. Very rarely: pseudomembranous colitis; convulsions, psychotic and other CNS-reactions; anaphylactic reac-

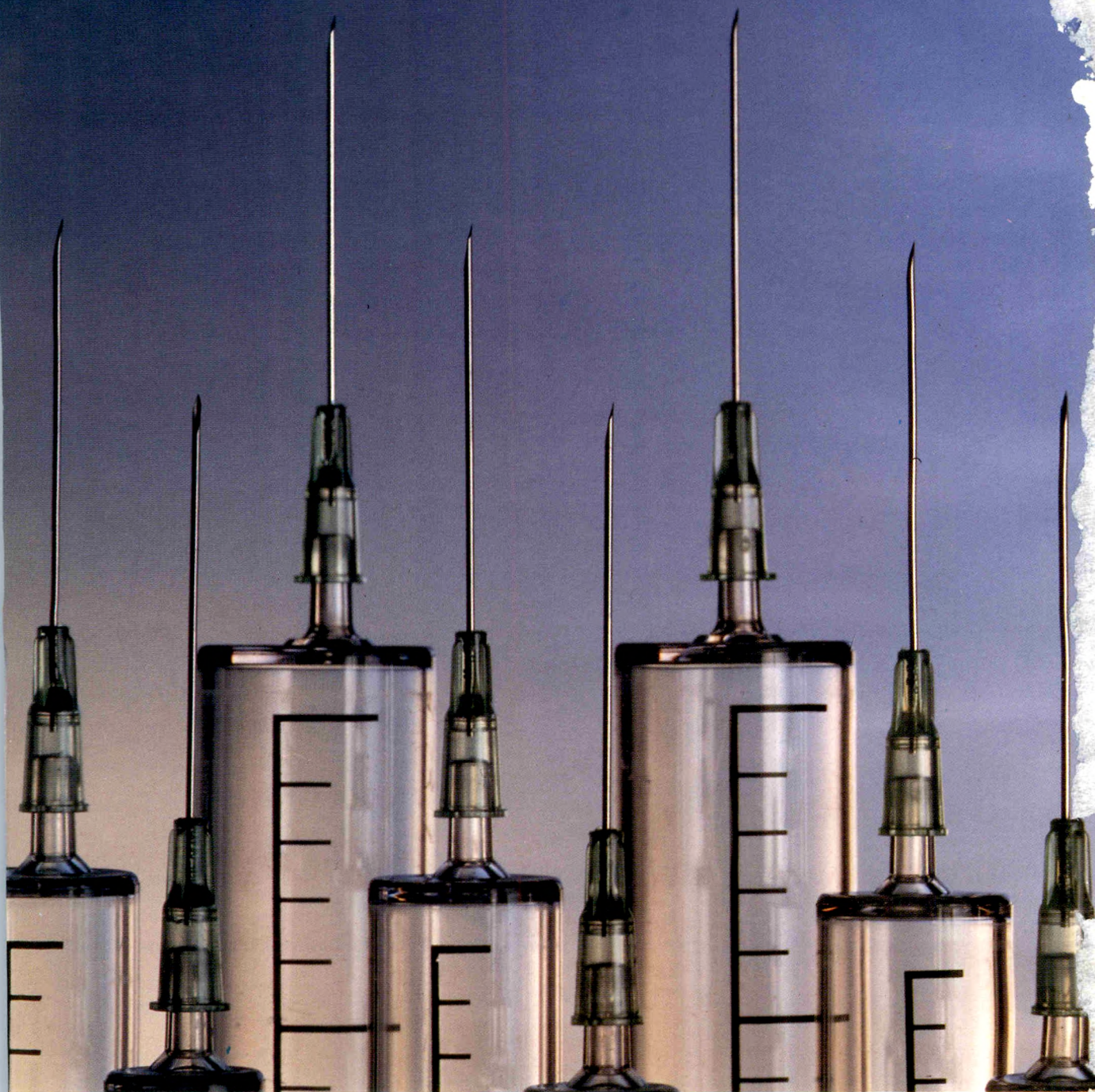
tions, including shock; Stevens-Johnson syndrome, interstitial nephritis, major liver disorders, including hepatic necrosis; photosensitivity; impaired kidney function, including transient kidney failure; transient hearing loss, ability to drive or operate machinery may be impaired. Local: phlebitis.

Full prescribing information available from:

Bayer AG,
Leverkusen,
Health Care Sector,
5090 Leverkusen,
FR Germany.

Bayer

Choose any number from the left..



AUGMENTIN clavulanate-potentiated amoxycillin. **INDICATIONS.** **Upper Respiratory Tract Infections** e.g. Sinusitis, tonsillitis, otitis media. **Lower Respiratory Tract Infections** e.g. Acute atypical pneumonia, bronchitis, lobar and bronchopneumonia, empyema, lung abscess. **Skin And Soft Tissue Infections** e.g. Boils/abscesses, cellulitis, wound infections, intra-abdominal sepsis. **Genito-Urinary Infections** e.g. Cystitis, urethritis, pyelonephritis, septic abortion, puerperal sepsis, pelvic infections, chancroid, gonorrhoea. **Other Infections** e.g. Osteomyelitis, septicaemia, peritonitis, postoperative infections. AUGMENTIN intravenous is also indicated for prophylaxis against infections which may be associated with major surgical procedures involving gastro-intestinal, pelvic, head and neck, renal, biliary tract and joint replacement surgery. **DOSAGE, Adults and Children over 12 years** IV injection/infusion – Usually 1.2g 8 hourly. In more serious infections increase frequency to 6 hourly intervals. **Children** IV Injection/infusion – Children 3 months–12 years. Usually 30mg/kg* AUGMENTIN infusion 8 hourly. In more serious infections, increase frequency to 6 hourly intervals. Children 3 months–12 years: 30mg/kg* AUGMENTIN every 12 hours in premature infants and in full term infants during the perinatal period, increasing to 8 hourly intervals thereafter. *Each 30mg AUGMENTIN contains 25mg amoxycillin and 5mg clavulanic acid. Treatment with AUGMENTIN should not be extended beyond 14 days without review. **CONTRA-INDICATION.** Penicillin hypersensitivity. **PREGNANCY AND LACTATION.** Changes in liver function tests have been observed in some patients receiving AUGMENTIN. The clinical significance of these changes is uncertain but intravenous AUGMENTIN should be used with caution in patients with evidence of severe hepatic dysfunction. In patients with moderate or severe renal impairment AUGMENTIN dosage should be adjusted as recommended in the Package Insert. **USE IN PREGNANCY AND LACTATION.** Use of AUGMENTIN in pregnancy is not recommended unless considered essential by the physician. During lactation, trace quantities of penicillin are detected in breast milk. **SIDE-EFFECTS.** Side-effects, as with amoxycillin, are uncommon and mainly of a mild and transitory nature. Diarrhoea, pseudomembranous colitis, indigestion, nausea, v.

...or the one that is right

iv AUGMENTIN

clavulanate-potentiated amoxycillin

A spectrum of power, an injection of strength

IV Augmentin has been shown to be effective against the resistant bacteria that defeat most ordinary antibiotics, allowing it to replace standard combination therapies.¹⁻⁹

Which makes it an outstandingly powerful and reliable antibiotic.

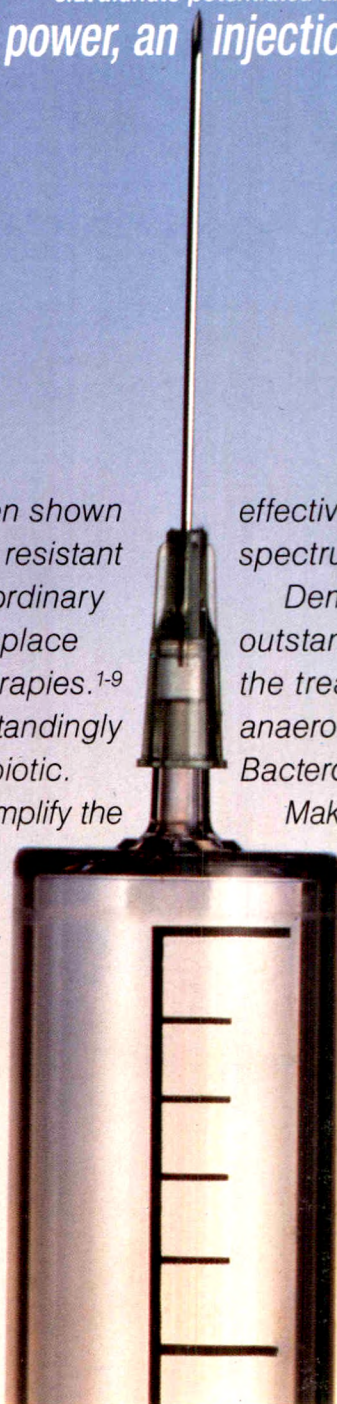
An antibiotic that can simplify the management of clinical and surgical infection.

IV Augmentin is highly

effective due to a remarkably broad spectrum of activity.²

Demonstrating consistent and outstanding clinical success in the treatment of both aerobic and anaerobic infection, including *Bacteroides*.²

Making it a powerful single choice for the first-line treatment of infection or reliable surgical prophylaxis.³⁻¹⁰



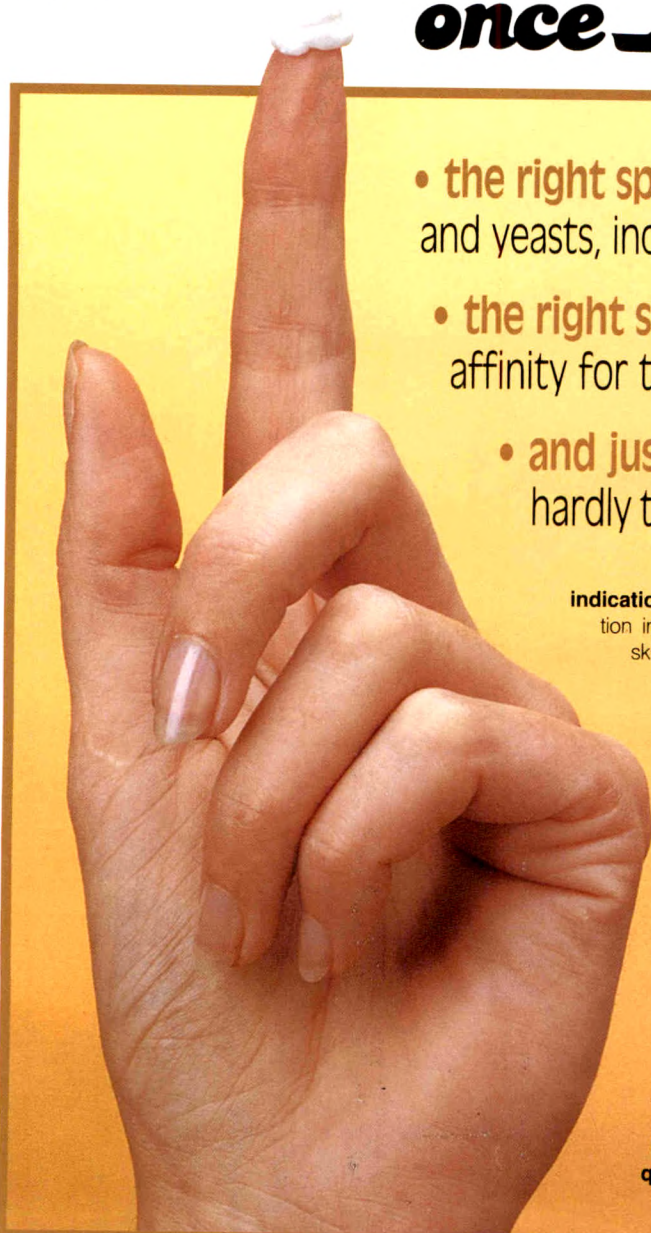
diarrhoea have been reported. Phlebitis at the site of injection has also been reported. Urticarial and erythematous rashes sometimes occur but their incidence has been particularly low in clinical trials. A urticarial rash suggests penicillin hypersensitivity and treatment should be discontinued. Erythematous rashes are frequently mild and transient but may be severe when associated with infectious mononucleosis, in which case treatment should be discontinued. Rare cases of erythema multiforme, Stevens-Johnson syndrome and an occasional case of exfoliative dermatitis have been reported and occasionally fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Hepatitis and cholestatic jaundice have been reported. **AVAILABILITY.** 600mg AUGMENTIN intravenous vials: containing 500mg amoxycillin and 100mg clavulanic acid. 1.2g AUGMENTIN intravenous vials: Each containing 1g amoxycillin and 200mg clavulanic acid. In IV presentations amoxycillin is present as sodium salt and clavulanic acid is present as the potassium salt. Each 1.2g vial contains approximately 1.0 mmol of potassium and 3.1 mmol of sodium. Not all presentations are available in every country. Further information is available on request from SmithKline Beecham Pharmaceuticals International, Brentford, England. AUGMENTIN is a product of research from SmithKline Beecham Pharmaceuticals International, Brentford, England. **REFERENCES:** 1. Green-Thompson RW et al, Proc 13th ICC Vienna 1983; **(79):** 17. 2. Asbach HW et al, Excerpta Medica 1980; **ICS 544:** 173. 3. Tehan S, Whittaker J, Surg Res Commun 1989; **6:** 97. 4. Levi D et al, Pharmatherapeutica 1989; **5:** 355. 5. Staker J, Tehan S, J Drug Dev 1989; **2** (Suppl 1): 71. 6. Asbach HW et al, Proc 13th ICC Vienna 1983; **70:** 30. 7. Croydon EAP et al, Chemotherapia 1985; **4** (Suppl 2): 168. 8. Martini M et al, Data on file, Beecham Pharmaceuticals. 9. Ploechl E, Huber EG, J Int Med Res 1986; **14** (3): 153. 10. Drumm J et al, Br J Surg 1985; **72** (7): 571.

Beecham
Pharmaceuticals
BRENTFORD ENGLAND

001/3/1/178/90

THE POWER OF KETOCONAZOLE IN A TOPICAL FORM

TRADEMARK **Nizoral** *cream* (ketoconazole 2%) **once-a-day**



- **the right spectrum:** dermatophytes and yeasts, including *Pityrosporum spp.*
- **the right site of action:** persistent affinity for the stratum corneum
- **and just once-a-day:** patients can hardly think of greater convenience

indications: Nizoral *cream* is indicated for topical application in the treatment of dermatophyte infections of the skin: tinea corporis, tinea cruris, tinea manus and tinea pedis, as well as in the treatment of cutaneous candidosis and tinea (pityriasis) versicolor.

contra-indications: Nizoral *cream* is contra-indicated in individuals who have shown hypersensitivity to any of its ingredients.

warnings: Nizoral *cream* is not for ophthalmic use. **adverse reactions:** Nizoral *cream* does not produce detectable blood levels after topical application. A few instances of irritation and burning sensation have been observed.

dosage and administration: Nizoral *cream* should be applied to affected areas once daily. Treatment should be continued for a sufficient period, at least until a few days after disappearance of all symptoms. **how supplied:** Nizoral *cream* (i.e. 20 mg ketoconazole per g cream) is supplied in 15 and 30 gram tubes. **Full prescribing information available on request.**



ANNALS OF SAUDI MEDICINE

TABLE OF CONTENTS

Volume 11 Number 3

May 1991

EDITORIAL

- Treating Children with Chronic Renal Failure: A Perspective
Tej K. Mattoo 253

ORIGINAL ARTICLES

- The Pattern and Outcome of Burn Injuries at a Burn Unit in Saudi Arabia: Retrospective Analysis of Consecutive 501 Patients
Mohammed M. Hegazy, Ezzeldin M. Ibrahim 255
- Patterns of Accidental Fractures and Dislocations in Children in Riyadh, Saudi Arabia
Abdulhalim A. Badr 260
- Pena-Shokeir Phenotype: A Lethal Pattern of Multiple Congenital Anomalies
Ahmed Warda, Hassan Abduljabbar, Hassan Ghafouri,
Abdullah H. Basalamah 264
- Incidence of Major Infection in Sickle Cell Pediatric Patients at Qatif Central Hospital
Hussain Ali Abu-Srair, Ali Magzoub El-Bashier,
Ibrahim S. Al-Dabous, Mohamed Al-Khater 267
- Morphological and Immunologic Pattern of Blastic Transformation in Chronic Myeloid Leukemia in Saudi Arabia: Study of 90 Transformations Among 248 Patients
George T. Roberts, M. Andrew Padmos, Hugh Clink,
David G. Spence, Peter Ernst, Kirtikant V. Sheth 271
- Current Procedures for Bladder Substitution and Urinary Diversion at King Faisal Specialist Hospital and Research Centre
Torsten Sundin, Shahid Rafiq, Bo Johan Norlen, Göran Alhgren 276
- Pattern of Cancer at Asir Central Hospital, Abha, Saudi Arabia
Abdur Rauf Khan, Nazir K. Hussain, Abdulaziz Al-Saigh,
Tarek Malatani, Anwar A. Sheikha 285
- Hypercalcemia in Active Pulmonary Tuberculosis
Sulaiman A. Al-Majed, Riad Sulimani, Faisal Al-Kassimi,
Lalit Pandya, Sameer Huraib, Nasser Al-Sharif 289
- Pulmonary Tuberculosis in Diabetic Patients
Lalit Pandya, Nasser Al-Sharif, Ali Maraey, Sulaiman Al-Majed,
Mahmood El-Sakka 293
- Acute Renal Failure in Neonates: A Prospective Study
Howaida M.A.M. Al Idressy, Omer B. Abdel Basit, Khalid N. Haque,
Murtala B. Abdurrahman 297
- Insulin-Dependent Diabetes Mellitus in Children: Familial and Clinical Patterns in Riyadh
Hussein Salman, Ahmed Abanamy, Basset Ghassan, Mohammed Khalil 302
- Meningitis in Children of Elmadina Elmunawara
Eisa Osman El-Amin, El-Fatih El-Shiek Musa, Sabah Ali Yousif 307
- Measles Vaccine Failure
Ahmed Abanamy, Mohammed Khalil, Hussein Salman,
Mahmoud Abdulazeem 311

Mantoux Reaction Survey Conducted in the Northern Region of Saudi Arabia	
Feisal Al-Kassimi, Anwar Abdullah, Ibrahim Al-Orainey, Mohamed Al-Hajjaj, Essam Al-Deen Abdul Baghee, Abdul-Baree Baner	315
Urinary Tract Infection in Pregnancy	
Hassan Abduljabbar, Rajaa A. Moumena, Hisham A. Mosli, Ahmed S. Khan, Ahmed Warda	322
SPECIAL COMMUNICATIONS	
Evaluation of Students' Performance and Examination Procedures in Final Certifying Examinations in Internal Medicine (1982-1988)	
Ezzeldin M. Ibrahim, Hassan Y. Al-Idrissi, Hussain M. Al-Freihi, Yussuf M. Al-Gindan	325
An Appraisal of the Utilization of Antenatal Services in Primary Health Care	
Abdulaziz Nasser Al-Nasser	331
Public Attitude and Accessibility Concerning Kidney Donation Card and Living Related Donation in Riyadh, Saudi Arabia	
Sulaiman Al-Shammari	336
CASE REPORTS	
Pneumonia Due to Salmonella Typhimurium	
Mohamed Azher, Faisal El-Kassimi, Abdul Hamid Chagla	341
Intractable Diarrhea Due to Whipple's Disease in a Saudi: Report of a Case and Literature Review	
Dharmaraj H. Patil, Eric S. Boye	343
Hodgkin's Disease Involving the Urinary Bladder: A Case Report	
Ezzeldin M. Ibrahim, Mohammad B. Satti, Osama M. Koreich, Issa A. Al-Uqali, Fatma A. Al-Mulhim	349
Klinefelter Syndrome, Rare Variant 49, XXXXY	
Hussein Salman, Ahmed Abanamy, Nizzamudin Khan, Ghassan Basset, Afsar H. Choudhury, Mona O. El-Ruby	352
LETTERS TO THE EDITOR	355
ANNOUNCEMENTS	363

FORTUM...

or aminoglycoside combinations



The choice is simple

Fortum provides the extended spectrum required for monotherapy without the ototoxic and nephrotoxic side effects of aminoglycoside combinations.

Fortum is a simple and effective approach to hospital acquired infections.

FORTUM

CEFTAZIDIME

Abbreviated Prescribing Information

Presentation: Fortum for injection is supplied in vials containing 250 mg, 500 mg, 1 g and 2 g ceftazidime (as pentahydrate) with sodium carbonate. **Uses:** Fortum is a bactericidal cephalosporin antibiotic which is resistant to most beta-lactamases and is active against a wide range of Gram-positive and Gram-negative bacteria. It is indicated for the treatment of single infections and for mixed infections caused by two or more susceptible organisms. Fortum, because of its broad antibacterial spectrum, may be used alone as first choice drug, pending sensitivity test results. **Dosage and administration:** Adults: 1 g to 6 g i.m. or i.v. per day and by the i.p. route 125 to 250 mg per two litres of dialysis fluid (see Data Sheet for details). Neonates, Infants and Children: Up to two months: 25 to 60 mg/kg/day given as two divided doses has proved to be effective. In the neonate the serum half-life of ceftazidime can be three to four times that in adults. Over two months: 30 to 100 mg/kg/day given as two or three divided doses (see Data Sheet for details). In Impaired Renal Function: the dosage of ceftazidime should be reduced when the glomerular filtration rate (GFR) falls below 50 ml/min. An initial loading dose of 1 g may be given to patients with suspected renal insufficiency (See Data Sheet for details). **Contra-indication:** Fortum is contra-indicated in patients with known hypersensitivity to cephalosporin antibiotics. **Precautions:** Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins. Care is indicated in patients who have experienced an anaphylactic reaction to penicillin. Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with nephrotoxic drugs. Clinical experience with Fortum has shown that this is not likely to be a problem at the recommended dose levels. As with all drugs, Fortum should be administered with caution during the early months of pregnancy and in early infancy. Fortum is excreted in human milk in low concentrations. Fortum does not interfere with enzyme-based tests for glycosuria. Slight interference with copper reduction methods may be observed. Fortum does not interfere in the alkaline picrate assay for creatinine. Fortum and aminoglycosides should not be mixed in the same giving set or syringe. As with other broad spectrum antibiotics, prolonged use of Fortum may result in the overgrowth of non-susceptible organisms (e.g., *Candida*, *Enterococci*) which may require interruption of treatment or adoption of appropriate measures. **Side effects:** Fortum is generally well tolerated with only infrequent adverse reactions, e.g. pain and/or inflammation after i.m. administration and phlebitis and/or thrombophlebitis after i.v. administration, rashes, fever, pruritus, anaphylaxis, gastrointestinal disturbances, headache, dizziness, paraesthesia and bad taste. Transient changes in laboratory values may occur including: eosinophilia, a positive Coombs' test, thrombocytosis, leucopenia, thrombocytopenia and slight rises in hepatic enzymes.

Glaxo For full prescribing information see data sheet or contact: **Glaxomed Limited**, International House,
7 High Street, Ealing, London W5 5DB, ENGLAND

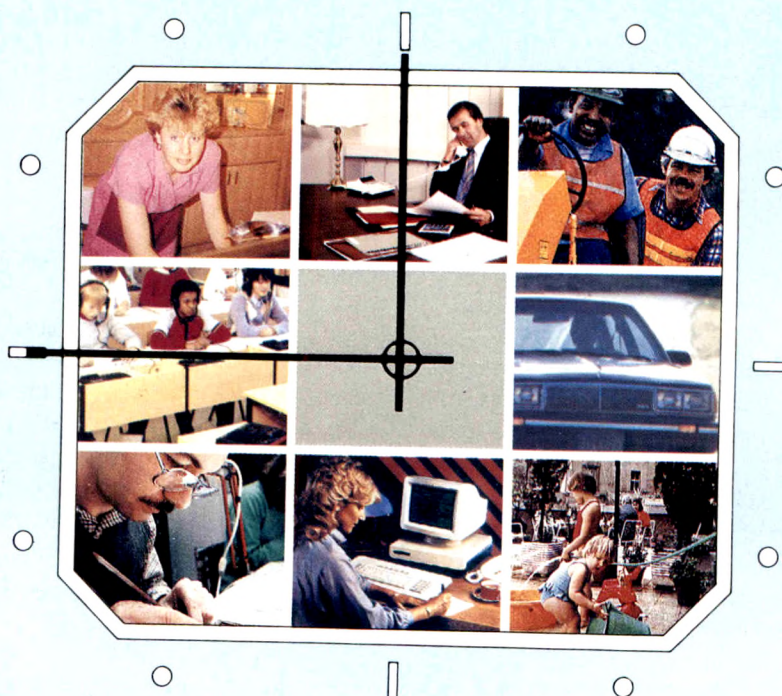
Fortum is a trade mark

Hismanal^{TRADEMARK}

astemizole

NEW

**approaching the ideal
in antihistamine therapy**



**The first once-a-day non-sedative
antihistamine effective in**

- seasonal allergic rhinitis
- perennial allergic rhinitis
- allergic skin conditions that
require an antihistamine therapy

Contains 10mg astemizole per tablet

Full product description available upon request from the manufacturer

JANSSEN the drug discovery company
PHARMACEUTICA Beerse Belgium

© Janssen Pharmaceutica

Editorial

TREATING CHILDREN WITH CHRONIC RENAL FAILURE: A PERSPECTIVE

A better understanding of chronic renal failure and the tremendous advances made in dialysis and organ transplantation have transformed the fate of children with end-stage renal disease (ESRD) from one of hopelessness to that of hopefulness. The survival rates of these children continue to improve steadily. It is, however, important to note that not only technical advances are responsible for this progress. Other factors have played an equally important role in enhancing the long-term prognosis and quality of life for the patients and their families. The aim of this editorial is to discuss briefly these issues in the context of rapidly advancing health care in the Kingdom.

A child with ESRD imposes numerous unexpected demands on the family. Hemodialysis involves regular attendance at the dialysis unit, whereas continuous ambulatory peritoneal dialysis (CAPD) involves a complicated technique of bag exchanges performed four times a day by a trained attendant, usually the mother. The administration of many drugs three to four times a day and a special dietary regimen add to the workload. Apprehensions and uncertainty about the patient's future add to parental anxiety, and the extra care needed by the affected child may be delivered at the expense of other siblings. Inability to cope with the physical and psychological stress can seriously jeopardize family life and this in turn affects the patient's care [1]. Such families must receive psychosocial support from the community in general and the social workers, health visitors, and clinical psychologists in particular.

Frequent and prolonged hospitalization deprives younger children of developing a normal relationship with their parents and siblings. This can lead to psychological and behavioral problems later in life [2]. Other children may also face problems with social adjustment. Their chances of making friends are compromised by irregular attendance at school, and this is compounded by apprehensions on the part of playmates and their

occasional taunting. The usual teenage stresses, lack of independence, and a need for strict dietary and drug compliance also contribute to their social maladjustment. A better understanding among the patient, parents, and the medical team supported by the expertise of a clinical psychologist helps prevent such problems.

Educating these children is important if they are to become useful members of society and develop economic independence. Patients on hemodialysis attend the dialysis unit three times a week and it is not always possible to integrate dialysis sessions with regular attendance at school. It is a common practice in many developed countries to have a resident teacher educate these children during hospital stays or during hemodialysis sessions. The teacher also liaises with the school and maintains continuity in the patient's education.

Proper diet is necessary in patients with chronic renal failure in order to slow down progression to ESRD, allow optimum growth, and improve uremic symptoms [3]. Educating parents to the dietary restrictions in such children requires the services of a properly trained nutritionist with a good knowledge of the local diet and an ability to communicate in the local language.

The initiation of chronic dialysis is only the beginning of a long and arduous process that includes technical difficulties and complications from dialysis, the organization of a renal transplant, and post-transplant care and rehabilitation. It is therefore natural to question the relevance of dialyzing some children with multisystem involvement such as severe mental retardation in times of ethical and moral issues. The answer is not easy. To help parents make difficult and sometimes painful decisions, they must be given a full and honest understanding of the problem, taking into consideration their educational background, religious beliefs, and social circumstances.

A child with ESRD, as compared with an adult, is likely to suffer more developmental, psychological, and social problems, and ultimately

economic difficulties. The need of the hour is the participation of the community and a combined team approach by the medical staff, nutritionists, social workers, psychologists, educational services, and health visitors. Dialyzing or transplanting children without such a holistic approach is like a horse-drawn wheel-less carriage which may reach its destination but in an unpredictable form.

Tej K. Mattoo, MD, DCH, MRCP
Consultant Pediatric Nephrologist
King Fahad Hospital
Kingdom of Saudi Arabia National Guard
P.O. Box 22490
Riyadh 11426, Saudi Arabia

References

1. Mailick M. The impact of severe illness on the individual and family: an overview. *Soc Work Health Care* 1979;2:117.
2. Simons RC, ed. *Understanding human behavior in health and illness*, ed 3. Baltimore: Wilkins & Wilkins, 1985;140-7.
3. Chantler C. Nutritional assessment and management of children with renal insufficiency. In: Fine RN, Gruskin AB, eds. *End stage renal disease in children*. Philadelphia: Saunders, 1984;193-208.

Original Articles

THE PATTERN AND OUTCOME OF BURN INJURIES AT A BURN UNIT IN SAUDI ARABIA: RETROSPECTIVE ANALYSIS OF CONSECUTIVE 501 PATIENTS

Mohammed M. Hegazy, FRCS; Ezzeldin M. Ibrahim, MRCP, FRCPI

أجريت دراسة مراجعة على ٥٠١ حالة متتالية لمرضى تعرضوا لإصابات حروق وتمت معاينتهم خلال الفترة من يونيو ١٩٨٣م إلى ديسمبر ١٩٨٨م. كان أغلب المرضى من الشباب دون سن العشرين (٥٣٪)، وكانت نسبة الذكور بينهم ٦٥٪، ونسبة المواطنين السعوديين ٧٢٪. وقعت معظم إصابات الحروق نتيجة لحوادث منزلية (٧٥٪) فيما مثلت الحروق السطحية (بها أو سائل حار) ٥٥٪ من مجموع الحالات. وبلغت نسبة الوفيات في المستشفى لدى أول دخول ٨٪. وأمكن بإجراء تحليل على المتغيرات المتعددة تحديد عدة عوامل مستقلة ذات إنذار سيء: كزيادة المساحة الكلية للحروق وإصابات الاستنشاق والتهاب الوريد الخثاري والانتانمية والحروق المحيطية العميقة فوق الأطراف. وأمكن باستخدام عوامل الإنذار الوخيم هذه تصنيف المرضى على ثلاث فئات خطر تمثل كل منها اختلافاً واضحاً فيما يتعلق باحتمالات البقاء. وقد أسهمت هذه الدراسة في تقديم معلومات عن نماذج إصابات الحروق والعوامل الإنذارية والنتائج المترتبة عليها وذلك في وحدة مخصصة لمعالجة الحروق في المملكة العربية السعودية.

We retrospectively reviewed the cases of 501 consecutive patients with burn injuries who were seen between June 1983 and December 1988. The population consisted predominantly of young patients under 20 years of age (53%); 65% were males and 72% were Saudi nationals. Most burn injuries were the result of domestic accidents (75%) and scald burns were the cause in 55% of patients. There was an inhospital mortality of 8% during first hospitalizations. Multivariate analysis identified several independent adverse prognostic factors: increased total burn surface area, inhalation injury, thrombophlebitis, documented septicemia, and deep circumferential burn over the extremities. Using these poor prognostic factors, we were able to stratify patients into three risk categories, each representing a significant difference in the probability of survival. Our analysis yielded data about the pattern of burn injuries, prognostic factors, and outcome at a dedicated burn unit in Saudi Arabia.

Death due to burn injuries ranks second only to traffic accidents among all unnatural causes of death [1]. Morbidity and mortality statistics about burn injuries in developing countries are not

adequately documented in the English literature, and the only data available for the Kingdom of Saudi Arabia has only recently been reported [2]. This lack of adequate data prompted us to analyze the local experience in the management of burn patients, using material from a five-year period.

From the Department of Surgery (Dr. Hegazy), Plastic Surgery Unit, and Department of Medicine (Dr. Ibrahim), College of Medicine and Medical Sciences, King Faisal University, Al-Khobar.

Address reprint requests and correspondence to Dr. Hegazy: Plastic Surgery Unit, Department of Surgery, King Fahd Hospital of the University, P.O. Box 40004, Al-Khobar 31952, Saudi Arabia.

Accepted for publication 26 June 1990.

Material and Methods

A 10-bed critical care burn unit was opened in June 1983 at King Fahd Hospital of the University, and was designated to receive primarily all

burn patients living in the Eastern Province who would have previously gone untreated. This made possible the study of a concentrated group of patients with burn injuries. The study population included all consecutive patients with burn injuries admitted to the burn unit between June 1983 and December 1988.

Patient care was standardized according to the type and extent of injury. Patients with deep burns that involved the face or neck, those with burns incurred in a closed space, and those with burns that affected the nasal vibrissae routinely underwent direct laryngoscopy to determine possible upper respiratory tract injury. The presence of extensive laryngeal edema was considered an indication for elective intubation.

A burn surface area of greater than 15% in children and 20% in adults was considered an indication for use of the modified Baxter's formula [3]. Prophylactic systemic antibiotic coverage was not used routinely, except perioperatively when major burn wound excision was necessary. Large surface area wounds were managed surgically by staged excision and autografting, usually done 5 to 7 days after the burn injury.

A computerized data base was constructed using a personal computer. Several variables were tested for their unadjusted association with survival using the chi-square test. Covariates with $P \leq 0.10$ were included in the all-possible subset regression analysis to identify the "best" subset of predictor variables for survival. The "best" subset was selected using Mallow's C_p (coefficient) criteria, in which the "best" was defined as the smallest C_p [4].

Survival during hospitalization was estimated using the Kaplan-Meier method and was calculated from the date of admission to date of discharge or death [5]. The log-rank test of Mantel-Cox was used to compare the unadjusted differences in survival [6].

In all data analysis, $P \leq 0.05$ (two-tailed) was considered significant. Data analysis was carried out using P4F and P9R programs of the BMDP Statistical Software package [7].

Results

All 501 patients seen during the designated time period were evaluable for occurrence of complications and for survival. Mean age was 16.5 years.

Patients data are summarized in Table 1. Patients under 20 years of age constituted the majority (53%); 65% were male and 72% were Saudi nationals. The mean hospital stay was 3.89 weeks (range, 0.1–14).

Forty-one patients (8%) died during hospitalization as the result of their burns. The unadjusted effects of various variables on the probability of survival during hospitalization were examined. As shown in Table 1, the significant adverse prognostic factors were: older age, extensive burn, type of burn, and inhalation injury, as well as the occurrence of any of the following complications—thrombophlebitis, renal failure, documented septicemia, and deep circumferential burns of the extremities requiring escharotomy and hematemesis. Figure 1 demonstrates the survival probability plotted against the total burn surface area.

All unadjusted variables with $P \leq 0.1$ were included as explanatory variables in the all-possible subset regression analysis. The dependent variable was death versus survival during hospitalization. Increased total percentage of burn surface area, inhalation injury, thrombophlebitis, documented septicemia, and deep circumferential burn over the extremities were associated with a decreased likelihood of survival (Table 2). The resultant explanatory variables accounted for 63% of the variance in survival probability (R^2). The Mallow's C_p of the model was 6.09 with an F statistic of 171.89 (df, 495 and 5).

Based on these derived models, patients were categorized into three risk strata. The following variables were deemed of equal weight in classifying patients: extensive burn ($> 30\%$), inhalation injury, thrombophlebitis, deep circumferential burn over the extremities, and documented septicemia. Patients with none of the factors represented the low-risk group; those with one or two, the intermediate; and those with three to four, the high-risk group. Death occurred in one of the 380 patients considered a low-risk group (0.26%), 3 of 58 regarded as intermediate risk (5.2%), and 37 of the 63 high-risk patients (58.7%). Figure 2 shows the survival curves of the patients in the three risk categories. The difference between the three survival curves was estimated using the log-rank test and was highly significant at $P < 0.00001$.

TABLE 1. *Clinical characteristics and outcome of 501 burn patients.*

Variable	Outcome		Total	P value
	Survived(%)	No. died		
Age (yr)				
< 20	255(96)	10	265)	0.0001
21-50	182(88)	24	206)	
> 50	23(78)	7	30)	
Sex				
male	301(93)	23	324)	0.23
female	159(90)	18	177)	
Nationality				
Saudi	328(92)	32	360)	0.45
non-Saudi	132(94)	9	141)	
Percentage of total burn area				
< 15	329(99.7)	1	330)	< 0.0001
16-30	79(99)	1	80)	
31-50	35(90)	4	39)	
> 51	17(34)	35	52)	
Type of burn				
flame	152(82)	33	185)	< 0.0001
scald	264(99)	3	267)	
chemical	19(86)	3	22)	
electric	25(93)	2	27)	
Inhalation injury				
no	450(97)	14	464)	< 0.0001
yes	20(27)	27	37)	
Incidence site				
domestic	349(93)	27	376)	< 0.19
industry	111(89)	14	125)	
Thrombophlebitis				
no	438(94)	30	468)	< 0.0001
yes	22(67)	11	33)	
Renal failure				
no	453(93)	36	489)	< 0.0002
yes	7(67)	5	12)	
CBD ^a				
no	424(99)	6	430)	< 0.0001
yes	36(51)	35	71)	
Septicemia				
no	419(97)	12	431)	< 0.0001
yes	41(59)	29	70)	
Hematemesis				
no	456(93)	37	493)	0.0002
yes	4(50)	4	8)	

^aCircumferential deep burn of extremities which required escharotomy and/or fasciotomy.

TABLE 2. The adjusted regression analysis of outcome (all-possible subset regression analysis).

Prognostic variable	Regression coefficient	Standard error	Contribution to R ²
Extent of burn	0.0055	0.0006	0.069
Inhalation injury	0.3339	0.0396	0.052
Thrombophlebitis	0.2252	0.0354	0.029
CBC	0.1382	0.0347	0.012
Septicemia	0.0470	0.0310	0.002

CBD = circumferential deep burn of extremities.

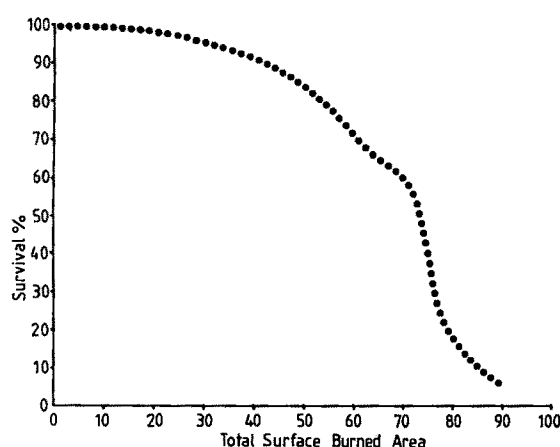


FIGURE 1. Survival proportions plotted against the extent of the burned surface area.

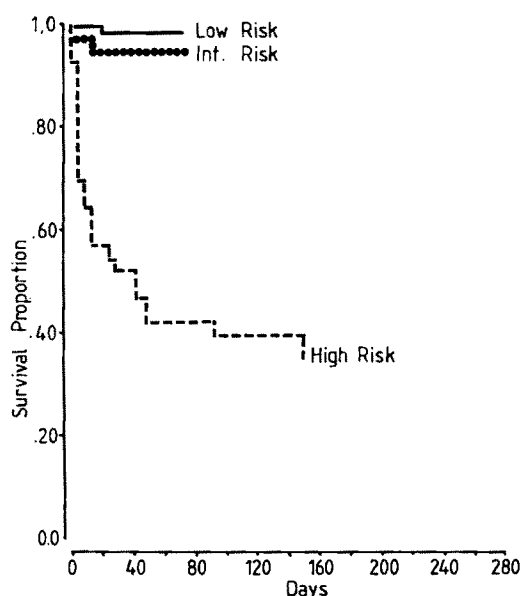


FIGURE 2. Kaplan-Meier survival curves for the three risk strata (low, intermediate, and high).

Discussion

Burn injuries represent a serious worldwide problem, as they account for considerable morbidity and mortality [1]. Accurate statistics on the incidence of burn injuries in the population of Saudi Arabia are not known because of a lack of regional or national burn registration.

Our data showed that the majority of our population (53%) were younger than 20 years and 44% were younger than 5 years. The mean age of the entire population was 16.5 years. The dominance of children and young adults in our series is comparable to that observed for burn units from other developing countries [8,9]; however, it differs from that reported for England and Wales [10]. The high prevalence of burns in males was also comparable to those from Cuba and Mauritius [11], but contrasts with that reported for Egypt [9].

The high incidence of domestic burn accidents (75%) is similar to the 71% and 79% reported from Nigeria and Kuwait, respectively [11,12]. Scald injuries were responsible for 55% of all accidents, and this high rate contrasts with those reported for Egypt [9], England and Wales [10], and Libya [13], where flame burns were the most common type of injury.

Survival analysis revealed that 8% of the patients died during hospitalization. The mortality reported from various studies of burn injuries varies considerably, from 5.2 to 25%, and depends on the nature of the study population and whether the data were derived from a dedicated burn unit or a general surgical ward [8-16]. The survival pattern in our patients (Figure 1) is comparable to those reported from other series [17-19]. The low mortality in our population could be attributed to several factors: (1) the dominance of young patients; (2) referral of all patients within hours of the accident; (3) treatment of all patients by trained staff in a specialized burn unit rather than in general surgical wards; and (4) a total burn surface area of less than 15% in 66% of all patients (330 of 501). The error inherent in assessing prognosis based on independent examination of variables rather than in combination has been previously emphasized [20,21].

The inverse relationship between the extent of burn and survival probability shown in our series is a well-established observation [22,23].

The negative effect of inhalation injury, proved by multivariate analysis, also agrees with data published from other centers [24,25]. The high mortality rate (73%) in patients with inhalation injuries is expected, due to the known deleterious influence of smoke inhalation on respiratory airways, microvascular permeability, and myocardial contractility [20].

None of the previously published studies identified thrombophlebitis as a negative prognostic feature, but in our study it may have become evident because those patients with extensive burns and with resulting lack of venous access who required cut-down procedures were made highly susceptible to suppurative thrombophlebitis. The use of intravenous plastic cannulas has also been linked with an increased risk of colonization by invasive microorganisms [27], and this was also true in our patients. Furthermore, suppurative thrombophlebitis often manifests itself only after systemic symptoms of sepsis arise, as dark discolored eschar can hide the early manifestations of thrombophlebitis.

A high incidence (15%) of deep circumferential burns over the extremities was noted in our series and this was associated with high mortality (49%). Deep circumferential burns of the extremities can cause severe ischemia in underlying muscle by producing compartmental compression syndrome [28].

Use of the prognostic factors identified in our series has been successful in categorizing the patient population into different risk strata, but our data should be validated in a prospective study.

Our data provide an epidemiological foundation concerning the pattern of burn injuries in a burn unit located in the Kingdom of Saudi Arabia. This information should provide baseline information for future comparison with data derived for other regions.

References

1. Feck G, Baptiste L. Burn injuries: epidemiology and prevention. *Accid Prev* 1979;2:129.
2. Report of first international workshop on burn injuries, epidemiology and prevention, in collaboration with the World Health Organization, November 6-8, 1985, New Delhi, India. South East Asia Regional Office Bull Burn Injuries 1988;5:1&2.
3. Baxter CR. Fluid volume and electrolyte changes of the early postburn period. *Clin Plast Surg* 1978;58:1313-1322.
4. Hocking RR. Criteria for selection of a subset regression: which one should be used. *Technometrics* 1972;14:967-70.
5. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958;53:457-81.
6. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163-70.
7. Dixon WJ, et al. *BMDP Statistical Software*. Berkeley: University of California Press, 1985.
8. Sowemimo GOA. Burn injuries in Lagos. *Burns* 1982;9:280-3.
9. Moustafa MF, Borhan A, El-Tahan A, Abdel-Fattah AM. An analytical study of 850 burns admitted to the burn unit of Alexandria Medical School. *Bull Alexandria Fac Med* 1972;329-36.
10. Muir IFK, Barclay TL. *Burns and their treatment*. London: Lloyd-Hoke, 1962;2.
11. Chaurosia AR. Mortality from burn in developing countries. *Burns* 1982;9:184.
12. Bang RL, Mosbah KM. Epidemiology of burns in Kuwait. *Burns* 1988;14:194.
13. Akhtar M, Gang RK. Epidemiology of burns in Benghazi, Libya. *Burns* 1981;7:351-6.
14. Johnson G, Nylan B, Olander K. Burn unit in Stockholm: a report on patients treated 1971-1975 for acute burn injuries. *Scand J Plast Reconstr Surg* 1980;14:171-7.
15. Mallo CN, Misgar MS, Khan M, Singh S. Analytical study of burns in Kashmir. *Burns* 1983;9:180-3.
16. Moustafa MF, Borhan A, El-Tahan A, et al. A retrospective study of 1896 burn patients. *Bull Alex Fac Med* 1979;15:59-66.
17. Cornell RG, Feller I, Roi LD, et al. Evaluation of burn care utilizing a national burn registry. *Emerg Med Serv* 1978;7:107.
18. Evaluation of emergency medical services with a national burn registry: final report to the national center for health services research (Grant number HS-10906). Submitted by the University of Michigan, Department of Biostatistics, and to the National Institute for Burn Medicine, Ann Arbor, Michigan 1979.
19. Feller I, Flanders S. Mortality review based on profile analysis. *Qual Rev Bull* 1979;5:30-5.
20. Bowser BH, Cadwell FT, Baker JA. Statistical methods to predict morbidity and mortality: self-assessment techniques for burn unit. *Burns* 1983;9:318-26.
21. Zawacki BE, Azen SP, Imbus SA, Chang YT. Multifactorial probit analysis of mortality in burned patients. *Ann Surg* 1979;189(1):1-5.
22. Bull JP. Revised analysis of mortality to burns. *Lancet* 1971;2:133-4.
23. Feller I, Tholen D, Dornell RG. Improvements in burn care, 1976 to 1979. *JAMA* 1980;244:2074-8.
24. Herndon DN, Barrow RE, Traber DL, et al. Extravascular lung water changes following smoke inhalation and massive burn injury. *Surgery* 1987;102(2):341-9.
25. Divincenti FC, Pruitt BA Jr, Reckler JM. Inhalation injuries. *J Trauma* 1971;11:109-17.
26. Traber DL, Linares HA, Hendon DA, et al. The pathophysiology of inhalation injury: a review. *Burns* 1988;5:357-64.
27. Pruitt BA, Stein JM, Foley FD, et al. Intravenous therapy in burn patients: suppurative thrombophlebitis and other life-threatening complications. *Arch Surg* 1970;100:399-404.
28. Kingsley NW, Stein JM, Levenson SM. Measuring tissue pressure to assess the severity of burn-induced ischemia. *Plast Reconstr Surg* 1979;63(3):404-8.

PATTERNS OF ACCIDENTAL FRACTURES AND DISLOCATIONS IN CHILDREN IN RIYADH, SAUDI ARABIA

Abdulhalim A. Badr, FRCS

أجريت دراسة على ١٤٥٦ حالة من حوادث الكسر والخلع المؤكدة لدى الأطفال لتحديد أنماط تلك الكسور والخلوع وتوزيعها حسب السن والجنس وأسبابها ومدى إمكانية الوقاية منها. كانت الخلع نادرة (أقل من ١٪ من الإجمالي) بينما كانت كسور الطرفين العلويين أكثر من كسور الطرفين السفليين، وفيما يلي أكثر الكسور تصادفاً: كسور الساعد (٣٩,٦٪)، العضد (١٢٪)، الترقوة (١١٪)، الطنبوب والشظية (١٠,٦٪)، الفخذ (٥,٦٪). كانت نسبة الذكور إلى الإناث ٢,٣ : ١، وبدا أن خطر الإصابة يزداد لدى الأطفال في سن ما قبل المدرسة (٢ - ٦ سنوات) واليا فعين (١٢ - ١٤ سنة)، وكانت الحوادث غير المرورية هي السبب في ٩٣٪ من الحالات. وقد خلصنا إلى القول بأن مراقبة الصغار وتثقيف الكبار صحياً يقللان من وقوع هذه الإصابات.

A study of 1456 confirmed cases of accidental fractures and dislocations in children was conducted to examine the patterns of fractures and dislocations, age and sex distribution, and the causes and possible prevention of such mishaps. Dislocations were uncommon and accounted for less than 1% of the total. There were more fractures of the upper than lower limbs, and the most commonly encountered fractures were: forearm (39.6%), humerus (12%), clavicle (11%), tibia and fibula (10.6%), and femur (5.6%). The male to female ratio was 2.3 to 1, and the risk of injury appeared to be higher in preschool children (2-6 years) and in adolescents (12-14 years). Non-road traffic accidents were the cause of 93% of the cases. It was concluded that supervision of the younger age groups and health education of the older age groups may decrease the incidence of injury in children.

Accidents in general and road traffic accidents in particular remain a major community health problem and a major cause of death in children over the age of one year [1]. In Saudi Arabia, road traffic accidents are the main cause of death [2] and the second major medical problem next to infection [3]. Apart from mortality, accidental fractures are probably one of the most reliable parameters of danger factors in the lives of children [4].

This study is based on a computer analysis of 1456 cases of accidental fractures and dislocations initially treated at Riyadh Central Hospital during

1986. The aims were to study and analyze the patterns of fractures and dislocations, the age and sex distribution, and the causes, as well as to discuss possible preventive measures of accidental injuries.

Patients and Methods

The hospital records of patients who were initially treated or admitted to Riyadh Central Hospital with musculoskeletal injuries during 1986 were retrieved. Because the number of cases was very large, only patients seen in the even months of the year were considered. Soft tissue injuries were excluded and only cases of confirmed fracture or dislocation in patients below the age of 14 years were included.

The following data were collected: age, sex, nationality, cause of injury, type of fractures, site

From the Orthopaedic Division, College of Medicine, King Saud University & King Khalid University Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Badr: Division of Orthopaedics (49), King Khalid University Hospital, P.O. Box 7805, Riyadh 11472, Saudi Arabia.

Accepted for publication 30 June 1990.

(upper, middle, lower), side (right, left), associated injuries, and multiple fractures. The cause of injury was divided into two major groups. The first comprised road traffic accidents which included pedestrians, passengers, or drivers involved in motorcycle, car, and bicycle accidents. The second group consisted of all other non-road traffic accidents.

"Type of fracture," as used in this study, refers to a simple (closed) or compound (open) fracture. Associated injuries comprised head, chest, and abdominal injuries. The term "multiple fractures" was used to refer to cases in which there was more than one fracture. Fractures and dislocations were coded according to the WHO international classification of disease [5].

The collected data were fed into a microcomputer using a data base program (Reflex R), and later analyzed.

Results

A total of 4230 patients with a confirmed diagnosis of fracture dislocation were reviewed. Of these, 1456 were below the age of 14 years, and this group formed the study population.

Males made up 70% of the population and females, 30%. Non-road traffic accidents were the cause in 93% and road traffic accidents, in 7%. Saudis represented 69% and non-Saudis, 31%. Simple fractures were seen in 97% and compound, in 3%.

There were multiple fractures in 1.4% of the cases and associated injuries were encountered in 8% of the cases. Of the limb fractures, 55% occurred on the left side and 45% on the right.

Dislocations were uncommon and accounted for less than 1% of the total. There were more upper limb than lower limb fractures (Figure 1).

The most common five fractures encountered, in order of frequency, were the radius and ulna, humerus, clavicle, tibia and fibula, and femur (Table 1).

Dislocations

Dislocations were uncommon, accounting for less than 1% of the total. All patients but one were male. Non-road traffic accidents were the cause in 86%. None of the dislocations were compound, and associated injuries were encountered in 14%.

The most common dislocations were: elbow (29%), shoulder and acromioclavicular (21%), interphalangeal joints of the toes (21.5%), interphalangeal joints of the fingers (14%), and dislocation of the patella (14%).

Age and Sex Distribution

In analyzing age in relation to the incidence of injuries, it appears the risk of fractures is higher in preschool children (2-6 years) and adolescents (12-14 years), with an incidence of 35% and 17.5%, respectively.

Although males outnumbered females at all ages, it was noted that the male to female ratio

TABLE 1. Summary of findings in the most common upper limb fractures.

Location site	Percentage of total	Sex (M:F)	Nationality (Sd:O)	Cause (RTA:O)	Side (R:L)	Type (S:C)	Site			IAI
							Upper 1/3	Middle 1/3	Lower 1/3	
Radius & ulna	39.6	2.5:1	69:31	2.98	45:55	100:0	3.5%	54.5%	42%	3.5%
Humerus	12	1.3:1	70:30	3.5:96.5	48:52	98.9:1.1	11.4%	28.6%	60%	6.3%
Clavicle	11	2:1	68:32	3.7:96.3	45:55	100:0	--	--	--	3.7%
Tibia & fibula	10.6	2.6:1	68:32	20.6:79.4	44:56	94.8:5.2	9%	71%	20%	13.5%
Femur	5.6	2.2:1	70:30	42:58	46:54	97.5:2.5	22%	73%	5%	52%

M = male; F = female; Sd = Saudis; O = others; RTA = road traffic accident; R = right; L = left; S = simple; C = compound; IAI = incidence of associated injuries.

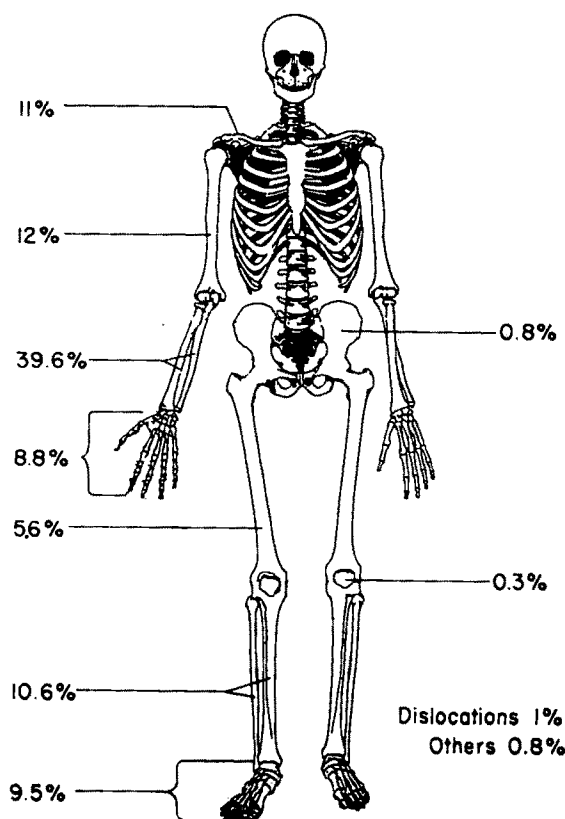


FIGURE 1. Frequency of fractures and dislocations.

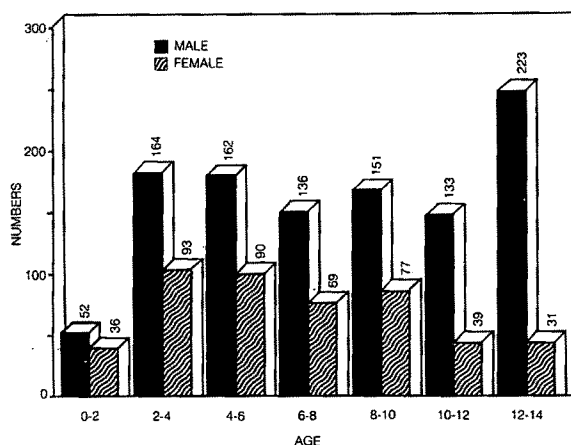


FIGURE 2. Age and sex distribution.

became more disproportionate as children grew older. At the 0-2 age group the ratio was 1.4:1, this increased to 2:1 in the 6-8 age group, 3.5:1 in the 10-12 age group, and 7:1 in the 12-14 age group. The age and sex distribution are summarized in Figure 2.

Cause of Injury

Non-road traffic accidents were the major cause of injuries in our series, accounting for 93% of the cases. Age and sex showed no association with the cause of injury.

A high percentage of lower limb fractures were the result of road traffic accidents, i.e., 42% of the femoral and 20.6% of the tibial and fibular fractures. Conversely, only 2% of the forearm fractures, 3.5% of the humeral fractures, and 3.7% of the clavicular fractures were the result of road traffic accidents.

Discussion

The patterns of accidental fractures and dislocations in the present study have confirmed the general impression that dislocations are uncommon [6]. Similarly, multiple and compound fractures were also uncommon in children, occurring in 1.4% and 3% of the cases, respectively. This finding could be explained by the fact that most of the fractures were caused by non-road traffic accidents.

Upper limb fractures were more common in our series than were lower limb fractures, and the most commonly encountered fractures were those of the forearm, arm, clavicle, leg, and femur, in order of decreasing frequency. We analyzed the age and sex distribution to determine the children most at risk for accidental fractures. Males were found to outnumber females in all age groups, and in steadily increasing numbers with each older age group. The pre-school age group and adolescents were most frequently involved.

Generally males are considered to have more active lifestyles and this leads to a higher incidence of injuries due to accident. This is particularly true in Saudi society where habit and tradition dictate a more protected and supervised lifestyle for females.

Although road traffic accidents as a cause of injury in this series were relatively uncommon, they were the cause of most serious injuries, constituting 42% of the femoral fractures and 20.6% of the tibial and fibular fractures. There was also a higher incidence of associated (multiple) injuries among these fractures. Road traffic accidents are deemed a major health problem in Saudi Arabia [2,3].

The overall findings in the present study suggest that the children at greatest risk are boys in the 2 to 6- and 12 to 14-year age groups. The radius and ulna are the most frequently involved sites of injury, and non-road traffic accidents are the most common cause.

There is no simple method of accident prevention, but certain measures, such as closer supervision of younger children at home, on the playground, and in school, as well as health education and instruction for older children, may decrease the incidence of injury. More research is also needed to identify potential accident hazards that pose a risk to Saudi children.

References

1. Sibert JR, Maddocks GB, Brown BM. Childhood accidents: an endemic of epidemic proportion. *Arch Dis Child* 1981;56:225-34.
2. Al-Qasabi QO, Mofarreh MA, Al-Bunyan AR, et al. Road traffic accident fatalities in Riyadh Central Hospital 1400-1407H (1980-1987). *Ann Saudi Med* 1989;9(3):237-40.
3. Mufti MH. Road traffic accidents as a Public Health problem in Saudi Arabia. *J Traffic Med* 1983;2:65-8.
4. Landin L. Fracture patterns in children. *Acta Orthop Scand [Suppl]* 1983;54:1-49.
5. Manual of the international statistical classification of diseases, injuries, and causes of death, 1977. Geneva: World Health Organization, 1977;473-99.
6. Sharrard WJW. *Paediatric orthopaedic and fractures*, ed 2. Oxford: Blackwell, 1979;1500-1662.

P 24, 757

PENA-SHOKAIR PHENOTYPE: A LETHAL PATTERN OF MULTIPLE CONGENITAL ANOMALIES

Ahmed Warda MD, PhD; Hassan Abduljabbar, MD, FRCS(C);
Hassan Ghafouri, MD, Facharzt (Paed);
Abdullah H. Basalamah, MD, MBBCh, MRCOG, FRCOG

نمط (بنيا - شقين) نمط ظاهري فريد ومتفاوت المظهر من الشذوذات الخلقية المتعددة غير المتوافقة مع الحياة. ويستعرض هذا المقال بالتفصيل تاريخ عائلة أنجبت شقيقين ينطبق وصفهما على نمط (بنيا - شقين) ويؤكد صحة المعايير المتخذة لتحديد النمط الظاهري، إضافة إلى موجودات غريبة تظهر في التصوير فوق الصوتي في فترة الحمل وقد نشر إلى التشخيص.

Pena-Shokeir phenotype is a unique pattern of lethal multiple congenital anomalies with variable expression. The history of a family in which two sibs conform to Pena-Shokeir phenotype is detailed and substantiates the criteria for definition of the phenotype. The addition of a peculiar ultrasound presentation in the antenatal period may indicate the condition.

There are more than a thousand proven mendelian disorders. They may be dominant or recessive and may involve either autosomes or sex chromosomes. The appearance of a recessive autosomal disorder implies that the parents, who look normal, must be carriers of the character trait. The offspring may be normal, a carrier, or affected in a 1:2:1 ratio, and consanguinity increases the likelihood of expression [1].

Pena-Shokeir phenotype is a rare, inherited, autosomal recessive condition, characterized by a prenatal onset degenerative disorder of the neurons and associated with multiple system defects that present an unusual antenatal sonographic picture. This was the second abnormal fetus born into the same family.

Case Report

The parents were a healthy couple, aged 25 and 20 years, who were first degree cousins. The

mother was gravida II, para I, +0. The product of the first pregnancy was an abnormal fetus with fetal ascites and hydrops shown by ultrasound (U/S) examination at 24 weeks. Intrauterine fetal death occurred one week later followed by spontaneous delivery of a macerated male fetus weighing 1550 kg that was grossly abnormal and hydropic.

Prior to the second pregnancy, possible etiological factors of the malformed fetus were sought. However, glucose tolerance test, VDRL, and TPH tests, TORCHE screen, and drug or radiation history yielded no clue as to a possible cause.

The couple was encouraged to embark on a new pregnancy, but as early as 21 weeks into this second pregnancy, U/S examination revealed abnormal brain texture.

U/S findings were described as the presence of multiple cystic areas in the brain substance, not confined to a ventricular system, but rather dispersed in the fore and hind brain (Figure 1). The mother was followed regularly every two weeks by U/S, which showed development of severe polyhydramnios at 23 weeks as well as other skeletal congenital abnormalities detected during pregnancy, including abnormal extremities, abnormal genitalia, and abnormal heart. However, as pregnancy progressed, there seemed to be a gradual disappearance of the previously seen

From the Departments of Obstetrics/Gynecology and Pediatrics, King Abdulaziz University, College of Medicine, Jeddah.

Address reprint requests and correspondence to Dr. Abduljabbar: Department of Obstetrics and Gynecology, King Abdulaziz University Hospital, P.O. Box 6615, Jeddah 21452, Saudi Arabia.

Accepted for publication 29 July 1990.

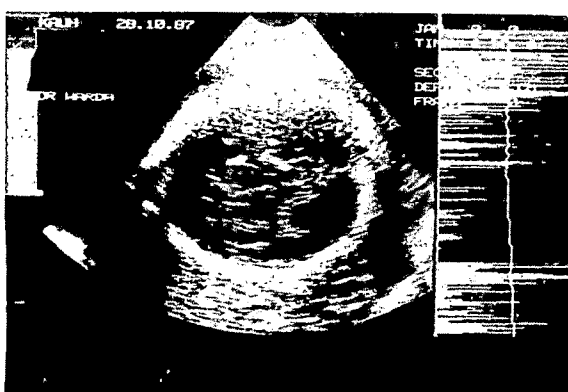


FIGURE 1. Ultrasound picture of the head at 24 weeks, showing cystic spaces extending into different anatomical areas of the brain and not confined to a ventricular system with normal biparietal diameter.

cystic brain areas, and the brain at 37 weeks showed only abnormal texture, but with none of the previously documented cystic areas. Although this finding fostered hope for a better prognosis, the existence of the other anomalies and progressive polyhydramnios made our approach to the worried parents very speculative.

At 38 weeks, there was spontaneous rupture of the membranes and the mother went into labor. The infant was delivered after 5 hours with no complications.

The mother was discharged the following day. At the time she was psychologically traumatized and refused to remain in the hospital after she had seen the child, on her own request.

The product of the pregnancy, a 2780-g male infant, had multiple congenital abnormalities and an Apgar score of 4 at 5 minutes. The gross appearance of the placenta was normal and the cord contained three blood vessels.

The head and neck showed scalp edema, prominent nasal bridge, puffy eyes, hypertelorism,

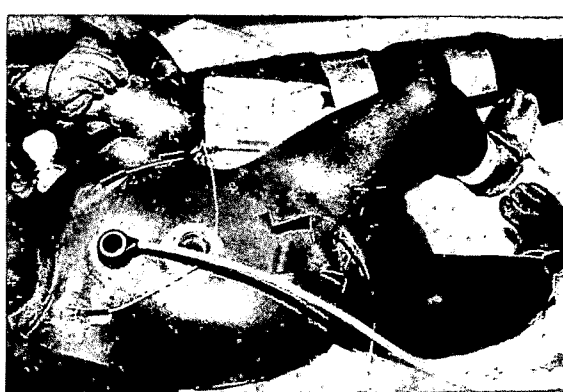


FIGURE 2. Pena-Shokeir syndrome phenotype.

mild micrognathia, low set ears, and a very short neck (Figure 2).

All limbs were affected by severe flexed contractures (arthrogryposis multiplex congenita) and the hands showed overlapping of the fingers on the thumb (captodactyly) with few palmar creases.

The thorax was short with scoliosis and there was poor air entry before inhalation. There was also bilateral cryptorchidism.

The child was intubated and transferred to the neonatal intensive care unit, where an array of complications developed during the ensuing 28 days, starting with generalized convulsions at 20 hours of age, and followed by jaundice on the second day. This required exchange transfusions on the fourth day because of a total bilirubin level of $340 \mu\text{mol/L}$.

A septicemic picture developed on the fifth day, and at that time, septic screen and hepatitis culture were negative, and TORCHE and immunoglobulin levels were normal. Antibiotic coverage was started.

The infant suffered arrest on the 10th day, but responded to resuscitation. Starting on the 20th day, he showed improvement that lasted for three days, but his condition once again deteriorated and there was fever and jaundice. He died at 28 days. Chromosomal analysis showed a normal 46 XY karyotype.

Discussion

In 1974, Pena and Shokeir [2] first reported the autosomal recessive, early lethal disorder that bears their name. At that time they estimated its frequency as 1 in 12,000 births, with a heterozygote frequency of 1:55.

Because of marked variability in the phenotype, each finding must be carefully investigated, pending establishment of final criteria.

The phenotype is considered to be an inherited prenatal-onset degenerative disorder of the neurons that leads to neuropathic muscular atrophy with consequent impairment of joint movement, resulting in a neural form of arthrogryposis multiplex congenita.

Failure of normal deglutition leads to polyhydramnios, and a neuromuscular deficiency in the diaphragm and intercostal muscles leads to pulmonary hypoplasia.

The phenotype overlaps that of trisomy 18, and the two must be differentiated in the neonatal period.

The appearance of brain cysts in the early part of pregnancy, and their subsequent disappearance, may be explained by degeneration and liquefaction of brain neurons, which would produce a echogenic picture similar to that of brain tissue. Moreover, postnatal U/S failed to detect brain abnormalities and postmortem examination would have been helpful, but unfortunately was unavailable.

The information now known about the syndrome should suffice for the prediction of the phenotype in future siblings. We believe our patient's first baby was affected by the same disorder, the pregnancy ending in intrauterine fetal death, witnessed in 30% of the cases [3].

The fact that our patient's sister is married to a brother of the patient's husband and the couple have two normal children indicates how selective an autosomal recessive gene can be. Pena and Shokeir described a second variety of the phenotype (type II), in which babies are born at term. In a few cases the dramatic full-blown pictures develops only over a matter of weeks to months [4]. The course is progressive and the babies die before five years of age, caused by pulmonary infections which are complicated by severe emaciation.

Recently there has been a good deal of confusion surrounding the terminology of this condition. Hall [5] postulated that "Pena-Shokeir" features do not constitute a specific syndrome, but rather represent a phenotype that is secondary to fetal akinesia or decreased in-utero movement, no matter what the cause. Such fetal akinesia/hypokinesia would lead to six types of phenotypic anomalies: intrauterine growth retardation, craniofacial anomalies, limb anomalies, pulmonary hypoplasia, short umbilical cords, polyhydramnios. As such, Pena-Shokeir phenotypes I and II are etiologically heterogeneous, although more than half of the published cases have been autosomal recessive, as was probably the case in our patient.

To try to elucidate further the nature of the disorder, it is important for all cases to be reported and described accurately, including further documentation by various investigations and post-mortem studies, whenever indicated.

References

1. Smith DW. Recognizable patterns of human malformation. Philadelphia: Saunders, 1982,136-7.
2. Pena SDJ, Shokeir MHK. Syndrome of camptodactyly, multiple ankyloses, facial anomalies and pulmonary hypoplasia: a lethal condition. *J Pediatr* 1974;85:373-5.
3. Pena SDJ, Shokeir MHK. Autosomal recessive cerebro-oculo-facio-skeletal (COFS) syndrome. *Clin Genet* 1974;5:285-93.
4. Shokeir MHK. Pena-Shokeir II syndrome: cerebro-oculo-facio-skeletal (COFS) syndrome. In: Myrianthopoulos N, ed. *Handbook of clinical neurology, Part II, Vol 45*. Amsterdam: North Holland Publishing Company, 1984;36-7.
5. Hall JG. Analysis of Pena Shokeir phenotype. *Am J Med Genet* 1986;25(1):99-117.

INCIDENCE OF MAJOR INFECTION IN SICKLE CELL PEDIATRIC PATIENTS AT QATIF CENTRAL HOSPITAL

Hussain Ali Abu-Srair, FRCP(C); Ali Magzoub El-Bashier, MRCPPath;
Ibrahim S. Al-Dabous, MD; Mohamed Al-Khater, MD

أدخل ٤٥٠ طفلاً يعانون من فقر الدم المنجلي إلى مستشفى القطيف المركزي خلال فترة سنتين من ٢٠ جمادى الأولى ١٤٠٨هـ إلى ٢٠ جمادى الأولى ١٤١٠هـ (٩ يناير ١٩٨٨م - ١٨ ديسمبر ١٩٨٩م). كان ٣٩ منهم يعانون من أحماج كبرى (انتان دموي، التهاب السحايا، أو التهاب العظم والنقي)، نسبة الوقوع ٨,٦٪. وأدخل إلى المستشفى خلال الفترة نفسها ٣٧٠٠ طفل لا يعانون من فقر الدم المنجلي وكان ٣٨ منهم يعانون من أحماج كبرى، نسبة الوقوع ١٪ ($P < 0.001$). توفي ثلاثة أطفال ممن يعانون من فقر الدم المنجلي، نسبة الإماتة ٢,٦٪ ($P < 0.002$). كانت أنواع السلمونية مسؤولة عن ١٢ حالة من الإنتان الدموي وثلاث حالات من التهاب العظم والنقي، بينما كانت العقديات الرئوية مسؤولة عن الإصابة بشماني حالات من الإنتان الدموي وحالة واحدة من التهاب العظم والنقي لدى المصابين بفقر الدم المنجلي. أما التهاب السحايا فقد سببته جراثيم مختلفة مثل العقديات الرئوية، السلمونية، والمكورات السحائية. ينبغي النظر في المضادات الحيوية التي شمل تأثيرها كلا من السلمونية والعقديات الرئوية لدى علاج جميع الأطفال المصابين بفقر الدم المنجلي حين يعانون من الحمى.

During the two-year period, 20 Jumada I 1408 (January 9, 1989) to 20 Jumada I 1410 (December 18, 1989), a total of 450 pediatric patients with sickle-cell anemia were admitted to the pediatric ward of Qatif Central Hospital. Thirty-nine patients had a major infection (septicemia, meningitis, or osteomyelitis), with an incidence of 8.6%. During the same period, 3700 non-sickle pediatric patients were admitted and 38 of them had a major infection, with an incidence of 1% ($P < 0.001$). Three patients died in the sickle cell group, for a case fatality rate of 7.6%, while only one patient in the control group died, for a case fatality rate of 2.6% ($P < 0.002$). *Salmonella* species were responsible for 12 cases of septicemia and three episodes of osteomyelitis, and *Streptococcus pneumoniae* was the source in eight cases of septicemia and one case of meningitis in sicklers. Meningitis was caused by different organisms, such as *Streptococcus pneumoniae*, *Salmonella*, and *Meningococcus*. Antibiotics that cover both *Salmonella* and *Streptococcus pneumoniae* must be considered in all children with sickle cell anemia who have a febrile illness.

Children with sickle-cell anemia have been known to have an increased susceptibility to severe bacterial infection, particularly caused by *Streptococcus pneumoniae*. Several abnormalities in the defense mechanisms of these patients have been noticed,

including functional hyposplenism [1], abnormalities in the alternative pathway of complement activation [2], and defective neutrophil function [3]. Septicemia and meningitis have been considered the major causes of death in sickle-cell patients [4-6], and the mortality from sickle-cell anemia is highest in the first five years of life [7-9].

The recent widespread availability of pneumococcal vaccines and improved programs of care for children with sickle-cell anemia have fostered hope that the high risk of life-threatening infection in these patients can be markedly

From the Departments of Pediatrics (Drs. Abu-Srair, Al-Dabous, Al-Khater), and Microbiology (Dr. El-Bashier), Qatif Central Hospital, Al-Jesh.

Address reprint requests and correspondence to Dr. Abu-Srair: Department of Pediatrics, Qatif Central Hospital, Eastern Province, P.O. Box 18439, Al-Jesh 31911, Saudi Arabia.

Accepted for publication 24 June 1990.

reduced. The mortality in these patients has been impressively decreased following the introduction of cord screening programs [10,11].

Material and Methods

During the two-year period of study, charts for all children with sickle-cell disease who were admitted to Qatif Central Hospital with clinical signs and symptoms of infections were reviewed retrospectively. Patients with sickle-cell disease were identified on the basis of a positive sickling test and hemoglobin electrophoresis using the Super Z Electrophoresis Kit (Helena Laboratories).

In patients with suspected septicemia, 3 ml of blood was drawn aseptically and divided into two bottles of the blood culture system (Bactec NR 660; Becton and Dickinson). Both bottles were incubated at 37°C for 7 days and read daily on a Bactec machine. Those showing signs of growth were Gram-stained and subcultured into blood agar, MacConkey agar, and chocolate agar, and incubated aerobically. The blood agar was incubated anaerobically. Organisms isolated after 24 to 48 hours of incubation were identified by conventional microbiological methods (Cowan's steel) [12] and AP120E was used for further identification of Gram-negative organisms. Each positive blood culture was evaluated according to the number of positive cultures, the type of organism isolated, the results of cultures from other sites, and clinical signs and symptoms, in order to differentiate between bacteremia and contamination.

In patients with suspected meningitis, lumbar puncture was done under aseptic conditions and

the samples delivered immediately to the microbiology laboratory. Gram's staining and latex agglutination were done. After centrifugation of the specimens, deposits were cultured in MacConkey and chocolate agar, incubated aerobically, and blood agar, incubated anaerobically, with 5 to 7% CO₂. All plates were read after 24 to 48 hours of incubation. Isolated microorganisms were identified by conventional microbiological methods. A portion of the cerebrospinal fluid was examined for estimation of glucose, protein, and chloride contents.

In patients with suspected osteomyelitis, blood culture and aspirate from the focus of infection were processed by routine methods.

Results

Table 1 lists the type of causative organisms found in sickle cell patients. There were 30 cases of septicemia, mainly due to *Salmonella* species and *S. pneumoniae*. Two of the affected patients died from *S. pneumoniae* infection. There were three episodes of meningitis caused by different organisms. One patient died from *S. pneumoniae* infection. *Salmonella* species were the cause in three cases of osteomyelitis, while one was caused by *S. aureus* and two showed no growth. The overall case fatality was 7.6%.

Table 2 shows bacterial distribution for the non-sickle group. There were 12 cases of septicemia mainly caused by *S. epidermidis*, while *H. influenzae* was the infecting organism in seven cases of meningitis. *S. aureus* infection was the main cause in the cases of osteomyelitis. The overall fatality rate was 2.6%.

TABLE 1. Major infections in sickle-cell patients.

Septicemia		Meningitis		Osteomyelitis	
Type of organism	No. of patients	Type of organism	No. of patients	Type of organism	No. of patients
<i>Salmonella</i> sp.	12	<i>S. pneumoniae</i>	1 ^b	<i>Salmonella</i> sp.	3
<i>S. pneumoniae</i>	8 ^a	<i>N. meningitidis</i>	1	<i>S. aureus</i>	1
<i>S. epidermidis</i>	5				
<i>S. aureus</i>	3				
<i>H. influenzae</i>	2	<i>Salmonella</i> sp.	1	No growth	2

^atwo died.

^bone died.

TABLE 2. Major infections in non-sickle-cell patients.

Septicemia		Meningitis		Osteomyelitis	
Type of organism	No. of patients	Type of organism	No. of patients	Type of organism	No. of patients
<i>S. epidermidis</i>	7	<i>H. influenzae</i>	7	<i>S. aureus</i>	5
<i>S. pneumoniae</i>	3	<i>N. meningitidis</i>	1	No growth	1
<i>S. viridans</i>	2	<i>Klebsiella</i> sp	1 ^a		
		<i>Serratia</i> sp.	1		
		<i>Aeromonas hydrophilia</i>	1		
		<i>S. pneumoniae</i>	1		
		No growth	1		

^adied.

TABLE 3. Distribution of microorganisms isolated in sickle-cell anemia in relation to age and sites.

Age group (yr)	<i>Salmonella</i> sp.			<i>S. pneumoniae</i>			<i>S. epidermidis</i>		
	Septicemia	Meningitis	Osteomyelitis	Septicemia	Meningitis	Osteomyelitis	Septicemia	Meningitis	Osteomyelitis
1-3	3	1	0	3	0	0	2	0	0
4-6	1	0	1	2	0	0	2	0	0
7-9	5	0	2	2	1	0	0	0	0
10-12	3	0	0	1	0	0	1	0	0

Table 3 shows the distribution of microorganisms isolated in the sickle-cell patients in relation to the age and site of infection. There was no significant difference in the distribution of cases of septicemia caused by *Salmonella* in relation to age, while there was only one case of *Salmonella* meningitis in the 1- to 3-year age group. *Salmonella* osteomyelitis occurred mainly in the 4- to 9-year age group.

Streptococcus pneumoniae was encountered in three patients in the 1- to 3-year age group, while there were two cases each in the 4- to 6-year and 7- to 9-year age groups. There was one episode in the 10- to 12-year age group.

Of the five cases of *S. epidermidis* septicemia, four were in patients in the 1- to 6-year age group, and only one was in the 10- to 12-year age group.

Discussion

Increased susceptibility to overwhelming bacterial infections is the leading cause of morbidity and mortality in patients with sickle-cell anemia, particularly in early childhood [13]. Sickle-cell

anemia in the inhabitants of the Eastern Province of Saudi Arabia has been reported to show only mild clinical manifestations, with only moderate hemolytic anemia [14,15]. Our study clearly demonstrated that the disease is not as benign as was thought. It is clear from our findings that the incidence of major infection in patients with sickle-cell anemia is higher than that in normal children (8.6% and 1%, respectively; $P < 0.001$).

Other investigations have emphasized the frequent occurrence of infections due to *S. pneumoniae* and *Salmonella* species [16-18]. We found that *Salmonella* species and *S. pneumoniae* were the cause in 20 of 30 cases (66%) of septicemia, and all were community-acquired infections. *S. epidermidis* was the cause in all five cases (16%) of septicemia. The organisms were isolated from more than one set of blood culture and the infections were clinically prominent; all five episodes were hospital-acquired infections and were related to the use of intravenous catheters.

H. influenzae type B was the causative organism in two episodes of septicemia in sickle-cell patients (6.6%), while no *H. influenzae* was iso-

lated in the children without sickle-cell anemia during the same period. Conversely, *H. influenzae* caused seven episodes of meningitis in the non-sickle cell group, but there was no case of meningitis caused by *H. influenzae* in the sickle-cell patients.

It has been shown that cord screening programs and the education of parents about sickle-cell anemia has led to a markedly reduced mortality [19,20]. Mortality rates of 30% [8] and 14% [21] have been reported for newborn screening programs in which neither education nor comprehensive medical follow-up was provided as part of the screening effort.

On the basis of these results, we conclude that the neonatal detection of sickle-cell anemia should be a high priority. Educating parents concerning the magnitude of the problem, along with penicillin prophylaxis during the first 3 to 5 years of life coupled with both pneumococcal and *H. influenzae* vaccine in sickle-cell patients, should be implemented. For children with sickle-cell anemia who have a febrile illness, it is important to choose an antibiotic that is effective for both *S. pneumoniae* and *Salmonella*.

References

1. Pearson HA, Spencer RP, Cornelius EA. Functional asplenia in sickle cell anemia. *N Engl J Med* 1969;281:293-6.
2. Johnston RB, Newman SL, Struth AG. An abnormality of the alternative pathway of complement activation in sickle cell disease. *N Engl J Med* 1973;288:803-8.
3. Hernandez DE, Gonzales N, Rios R, et al. Phagocytosis in patients with sickle cell disease. *J Clin Lab Immunol* 1983;12:137-40.
4. Robinson MG, Watson RJ. Pneumococcal meningitis in sickle cell anemia. *N Engl J Med* 1966;274:1006-8.
5. Pearson HA. Sickle cell anemia and serious infections due to encapsulated bacteria. *J Infect Dis* 1977;136(suppl):525-30.
6. Barret-Connor E. Bacterial infection and sickle cell anemia: an analysis of 250 infections in 166 patients and a review of the literature. *Medicine (Baltimore)* 1971;50:97-122.
7. Seeler RA. Deaths in children with sickle cell anemia. *Clin Pediatr* 1972;11:634-7.
8. McIntosh LS, Rooks Y, Ritchey AK, et al. Fever in young children with sickle cell disease. *J Pediatr* 1980;96:199-204.
9. Gatson M, Verter JJ, Woods G, et al. A randomized trial. *N Engl J Med* 1986;314:1594-9.
10. Scott RB, Harrison FL. Screening of the umbilical cord blood for sickle cell disease. Utilization and implementation. *Am J Pediatr Hematol Oncol* 1982;4:202-5.
11. Pearson H. A neonatal program for sickle cell anemia. *Adv Pediatr* 1986;33:381.
12. Cowan ST, Steel KJ. Manual for the identification of medical bacteria. Cambridge: Cambridge University Press, 1970;77-122.
13. Thomas AN, Pattison C, Serjeant GR. Causes of death in sickle cell diseases in Jamaica. *Br Med J* 1982;285:633-5.
14. Perrine RP, Brown MJ, Clegg JB, et al. Benign sickle cell anemia. *Lancet* 1972;2:1163.
15. Glep AP. Benign sickle cell disease in Saudi Arabia: survival estimates and population dynamics. *Clin Genet* 1979;15:307.
16. Barret Connor E. Bacterial infections and sickle cell anemia. *Medicine* 1971;50:97-112.
17. Robinson WG, Watson RJ. Pneumococcal meningitis in sickle cell anemia. *N Engl J Med* 1966;274:1006-8.
18. Seeler RA, Metzger W, Watson MA. Diplococcus pneumoniae infections in children with sickle cell anemia. *Am J Dis Child* 1972;123:8-10.
19. Edmond AM, Collis R, Darvil D, et al. Acute splenic sequestration in homozygous sickle cell disease: natural history and management. *J Pediatr* 1985;107:201-6.
20. Scott RB, Harrison DL. Screening of the umbilical cord blood for sickle cell disease: utilization and implementation. *Am J Pediatr Hematol Oncol* 1982;4:202-5.
21. Grover R, Normans S, Wethers D, et al. Newborn screening for hemoglobinopathies: the benefit beyond the target. *Am J Public Health* 1986;76:1236-7.

MORPHOLOGICAL AND IMMUNOLOGICAL PATTERN OF BLASTIC TRANSFORMATION IN CHRONIC MYELOID LEUKEMIA IN SAUDI ARABIA: STUDY OF 90 TRANSFORMATIONS AMONG 248 PATIENTS

George T. Roberts, MB, FRCPC; M. Andrew Padmos, MD, FRCPC;
Hugh Clink, MB, FRCPath; David G. Spence, MB, MRCPath;
Peter Ernst, MD; Kirtikant V. Sheth, MD

قمنا بدراسة نمط التحول الأرومي في ٩٠ مريضاً من أصل ٢٤٨ (٣٦٪) مريضاً مصابين بابيضاض نقوي مزمن ممن تمت معالجتهم في مستشفى الملك فيصل التخصصي ومركز الأبحاث بين عامي ١٩٧٥ و ١٩٨٨ م. كان متوسط العمر والعمر الوسطي لجميع المرضى ٣٨, ٢ و ٣٦ عاماً على التوالي. حضر أربعة من مرضى التحول التسعين (٤, ٤٪) في حالة تحول أرومي، بينما تطورت ٨٦ حالة من مرحلة إزمان واضحة المعالم. حدث التحول الأرومي اللمفاوي لدى تسعة وعشرين (٢, ٣٢٪) من المرضى، والنقياني لدى ثمانية وعشرين (١, ٣١٪)، والنقوي وحيد النوى لدى سبعة (٨, ٧٪)، والتحول وحيد النوى أو تحول الأرومات الحمر لدى (٤, ٤٪)، وتحول أرومة النواء لدى ستة (٧, ٦٪)، وتحول مختلط السلالات لدى عشرة (١, ١١٪)، كما تعذر تصنيف اثنين (٢, ٢٪). كانت الخلايا الأرومية اللمفاوية ايضاً ملفياً حاداً منتظم الانتشار (أي، إيجابي بالنسبة لمستضدات Ia و CD10)، في حين كانت التحولات النقيانية في غالبيتها سلبية بالنسبة لمستضدات (Ia). وكانت الأرومات ذات الأنماط الظاهرية المختلطة في غالبيتها إيجابية بالنسبة لمستضدات - Ia (٨ من ١٠)، مع إيجابية متغيرة بالنسبة لـ (CD10) ولواسمات النقيانيات/ الوحيدات. نستنتج من هذا أن نمط النوبة الأرومية في حالات ابيضاض الدم النقوي المزمن لدى المرضى السعوديين مشابه للنمط الذي يشاهد لدى المرضى في البلدان الأخرى، وأن إيجابية المستضد (Ia) السطحي لخلايا الأرومة اللمفية مؤشر يمكن الاعتماد عليه لتمييز النوبة اللمفاوية من النوبة غير اللمفاوية التي لا يمكن فيها عادة تبيان المستضد (Ia).

We examined the pattern of blastic transformation in 90 of 248 patients (36%) with chronic myeloid leukemia who were seen at the King Faisal Specialist Hospital and Research Centre between 1975 and 1988. The mean and median ages of all patients were 38.2 and 36.0 years, respectively. Four of the 90 transformants (4.4%) presented in blastic transformation, and 86 cases (95.5%) evolved from a well-defined chronic phase. Twenty-nine (32.2%) of the patients underwent lymphoid blastic transformation, while 28 (31.1%) were myeloid, seven (7.8%) were myelomonocytic, four (4.4%) were monocytic or erythroblastic, six (6.7%) were megakaryoblastic, ten (11.1%) were of mixed lineage, and two (2.2%) were unclassified.

From the Department of Pathology and Laboratory Medicine (Drs. Roberts, Sheth) and Department of Oncology (Drs. Padmos, Clink, Spence, Ernst), King Faisal Specialist Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Roberts: Department of Pathology, Division of Hematology, Victoria General Hospital, 5788 University Avenue, Halifax, N.S., Canada B3H 1V8.

Accepted for publication 13 June 1990.

able. The lymphoid blast cells were uniformly common acute lymphocytic leukemia (i.e., Ia and CD10 positive), whereas the myeloid transformations were predominantly Ia negative. Mixed phenotype blasts were also predominantly Ia positive (i.e., 8 of 10), with varying positivity for CD10 and myeloid/monocytic markers. We conclude that blast crisis in chronic myeloid leukemia occurs in Saudi patients in a pattern similar to that seen in patients elsewhere, and that surface Ia antigen positivity in lymphoblast cells is a reliable marker for differentiating lymphoid from nonlymphoid crisis, in which the Ia antigen is not usually demonstrable.

Chronic myeloid leukemia (CML) is a clonal malignant disorder, which affects a pluripotent hematopoietic stem cell [1]. The malignant change is accompanied or preceded by a cytogenetic change involving reciprocal transfer of genetic material between the q arm of chromosome 9 and the q arm of chromosome 22, resulting in the Philadelphia chromosome (Ph') [2]. The disease runs a chronic phase of varying length, usually no more than about 48 months, and terminates in a more acute type of leukemia or blast crisis [3]. The reason why the chronic phase of CML transforms to a particular lineage of acute lymphocytic leukemia (ALL) is not known, but such transformations usually follow lines that are the normal developmental lines of the hematopoietic stem cell. Recent attempts have been made to correlate the additional cytogenetic changes that accompany or precede blast crisis with the lineage of the blast cells, but definitive patterns have not emerged [4,5].

Material and Methods

The patients were referred to KFSH&RC from various regions of Saudi Arabia and the Middle East. Patients presenting with the diagnosis or suspected diagnosis of CML undergo a number of clinical, radiological, and laboratory procedures in order to establish the correct diagnosis. Over the years, between 1975 to the present, the diagnostic laboratory procedures have varied, depending on the advancement of technology. However, certain laboratory procedures have remained constant. These include peripheral blood complete blood counts (CBC) and determination of leukocyte alkaline phosphatase activity. Wright-Giemsa-stained smears of both peripheral blood and aspirated bone marrow were examined routinely by light microscopy. In most cases, hematoxylin-eosin-stained sections of bone marrow cores obtained by Jamshidi needle biopsy, as well as histological sections of aspirated bone marrow, were examined by light micro-

scopy. When applicable, silver-stained sections were also examined for reticulin content. Since 1983, all new patients, and those who were being followed, had their bone marrow examined for cytogenetic abnormalities by Giemsa banding, using standard techniques [6]. When patients showed clinical or laboratory evidence of transformation, their bone marrow and peripheral blood samples were examined using the described procedures. In addition, these specimens were subjected to special cytochemistry in an attempt to classify the type of blast cells in the transformation. The cytochemical stains included Sudan black B, periodic-acid Schiff, alpha naphthyl acetate esterase, naphthol ASD chloroacetate esterase, and acid phosphatase [7]. When classification could not be achieved by light microscopy alone, the blast cells were examined by electron microscopy in a Jeol 100B electron microscope, either untreated or after treatment for myeloperoxidase or platelet peroxidase using standard methods [8]. Since 1984, the blast cells of transformants were studied for surface immunophenotype using commercially obtained monoclonal antibodies derived from mouse ascitic fluid, using a previously described method [9].

Results

The study was conducted between June 1975 and December 1988. A total of 248 patients were either prospectively entered into the study or their material retrieved from the records of the Department of Pathology and Laboratory Medicine. The general characteristics of the patients, including age and sex, are summarized in Table 1. There were 142 males and 106 females. Their mean age was 38.2 years, with a median of 36.0 and mode of 30.0 years. The youngest patient was 3 years old and the oldest, 85 years. The age distribution is shown in Figure 1, with a distribution that is obviously skewed toward those under 50 years.

TABLE 1. 248 patients with chronic myeloid leukemia: age patterns.

Variables	Males	Females	Total
Number	142	106	248
Mean age $\pm$ SD (yr)	39.7 $\pm$ 16.5	36.7 $\pm$ 15.2	38.2 $\pm$ 16.4
Median age (yr)	39.5	35.0	36.0

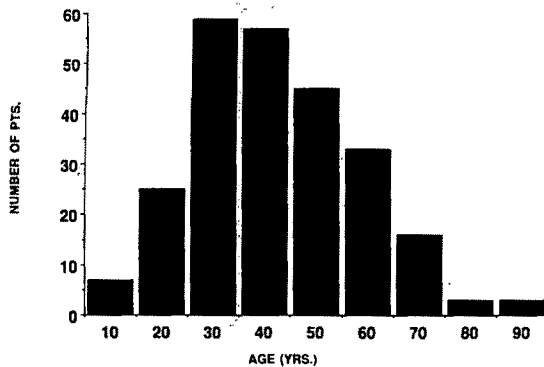


FIGURE 1. Age distribution at presentation in 248 Saudi patients with chronic myeloid leukemia. The median age is 39.5 years, which is considerably lower than the approximately 50 years cited for Western studies.

TABLE 2. Philadelphia chromosome in 175 patients with chronic myeloid leukemia.

Variables	Ph' positive	Ph' negative	Total
Number (%)	152(86.9%)	23(13.1%)	175
Mean age $\pm$ SD (yr)	38.9 $\pm$ 15.2	42.7 $\pm$ 19.7	39.5 $\pm$ 15.9
Median age (yr)	37.0	39.0	36.0

TABLE 3. Correlation between Ph' and LAP score.

Score	Ph'+	Ph'-	Total
LAP less than 13	108	10	118
LAP 13 and greater	16	4	20
Total	124	14	138

LAP = leukocyte alkaline phosphatase.

TABLE 4. Chronic myeloid leukemia: transformation in 90 cases.

	Age (yr)		
	Mean	SD	Median
Females (N = 43)	36.2	14.6	35.0
Males (N = 47)	38.6	15.4	40.0
All (N = 90)	37.4	15.0	36.5

Leukocyte alkaline phosphatase (LAP) scores were determined at diagnosis in 193 patients (77.8%), and in 164 (82.4%) the score was less than 13. The mean score was 8.8 (reference range, 13-35), with a median of 2 and mode of 0. The age and sex characteristics of this group were similar to those of the whole group.

Cytogenetic analysis was performed in 175 patients (70.1%), starting in 1983. Of those studied, 152 (86.9%) were Ph' positive (including complex translocations) and 23 (13.1%) were negative (Table 2). When correlated with LAP, it was found that most patients (108 of 124; 87%) who were Ph' positive also had lower than normal LAP scores (Table 3), which was highly significant at $P < 0.001$ using the chi-square test.

A total of 90 patients either presented in transformation (N = 4) or transformation evolved (N = 86) over varying periods. The general features are shown in Table 4.

The mean and median interval to transformation for the 86 patients who presented in an identifiable chronic phase were 27.6 and 20.5 months, respectively. Analysis of the patients by age showed that the time to transformation appeared to lengthen with increasing age in the 62 patients aged 10 to 50 years, but this relationship was not significant when subjected to regression analysis ($r = 0.13$, $P > 0.1$). However, for the 24 patients older than 50 years, the interval between diagnosis and transformation shortened with increasing age ($r = -0.45$; $P < 0.05$). The duration of survival after the onset of blast crisis will be discussed in a subsequent paper dealing with the overall clinical features of patients with CML.

Thirty-two patients out of 90 demonstrated additional chromosomal abnormalities that accompanied or preceded blastic transformations. The additional cytogenetic changes included additional Ph', extra chromosome 8 and isochromosome 17, as well as loss of chromosomes 5 and 7. Detailed analysis and correlations with blast phenotype will be the topic of a separate report.

Lymphoid transformation occurred in 29 patients (32.2%), and megakaryoblastic leukemia (M7) occurred in 6. There were ten patients with mixed lineage blasts and four patients with acute erythroleukemia (M6). Two patients had unclassifiable blasts, and the remainder of the patients had myeloid-type transformations (Table 5).

TABLE 5. Chronic myeloid leukemia: types of transformation and age patterns in 90 patients.

FAB type	M1/M2	M3	M4/M5	M6	MF	LYM*	Mixed	No
Number	27	1	11	4	6	29	10	2
Mean age (yr)	31.3	—	40.0	—	49.3	38.6	39.3	—
Median age (yr)	29.0	—	40	—	51.0	38.0	37.5	—

*FAB L1 and L2.

FAB = French-American-British classification.

TABLE 6. Cell surface markers in lymphoid transformation.

	Positive/negative ratio				
	CD20	CD19	Ia	CD10	Ph'
Males	2/3	5/1	7/0	6/1	7/0
Females	0/4	0/4	5/0	5/0	5/0

TABLE 7. Cell surface markers in lymphoid transformation.

	Positive/negative ratio					
	Ia	CD11	CD14	CD13	CD33	Ph'
Males	1/6	4/3	3/4	5/2	4/3	6/1
Females	1/3	2/1	3/0	3/1	2/1	3/1

A total of 12 cases exhibiting lymphoblasts were adequately phenotyped using a panel of monoclonal antibodies. All were positive for CD10 and Ia. The full phenotypic characterization of these cases is shown in Table 6. Determination of lymphoid lineage in the remaining 17 patients was based on light microscopy and cytochemistry findings.

There was adequate material for phenotypic characterization in 11 patients with myeloid transformation. Nine patients were negative for the Ia marker (Table 7). The two patients who were Ia positive were both M4.

The four patients who presented de novo in transformation all had the lymphoid form.

Discussion

We have followed 248 patients with CML over varying periods since June 1975, and have observed 90 transformations among them. The majority of the patients who were studied cytogenetically were Ph' positive (86.9%). There was no difference in age between the Ph'-positive and Ph'-negative patients (see Table 2). The patients were generally younger than those

reported from the West, probably reflecting the generally younger population in Saudi Arabia [E. Mahboubi, personal communication]. The LAP score was as predictive as Ph' in diagnosing CML; 81.6% of the patients studied had LAP scores less than normal, compared to 86.9% with Ph' positivity. Among Ph'-positive patients, 87.1% had low LAP scores (see Table 3).

The four patients who presented in transformation were identified on clinical grounds and by the presence of Ph', and all cases were of lymphoid origin. The problem of differentiating between CML presenting in lymphoblastic crisis and Ph'-positive ALL presenting de novo has not yet been resolved. The two entities are difficult to distinguish on clinical grounds, and superficially the Ph' chromosomes appear identical. Some authorities believe that the two conditions are the same entity [10,11]. However, recent work based on molecular biology has shown that, in typical Ph'-positive CML, the Ph' is a fusion gene that results from translocation of the ABL oncogene from its normal position on chromosome 9 to the break-point cluster region on chromosome 22 [12]. On the other hand, some cases of Ph'-positive ALL show a different kind of aberrant ABL gene that results from a translocation of the gene from its normal position on chromosome 9 to a point upstream from the break-point cluster on chromosome 22, and nearer the Ig lambda locus [12]. These findings may provide a means of differentiation between Ph'-positive ALL and Ph'-positive CML presenting in lymphoblast crisis.

The lymphoid-type transformation represented 32.2% (N = 29) of the total, a figure similar to those reported [4,5,13]. Of the patients tested, all were Ia and CD10 positive, with varying positivity for CD20 and CD19.

Forty (44.4%) of the transformations were of the myeloid type. Among these, the majority of the lineage assignments were based on light microscopy and cytochemical grounds, but in 11 patients it was possible to assign lineage based on cell surface markers as well. The blasts were usually nega-

tive for Ia (9 of 11) but positive for CD11, CD13, CD14, and CD33. The contrast between Ia negativity in myeloid transformations and Ia positivity in lymphoid transformations is similar to the observations of Fuscaldo et al [14], and may provide a relatively easy test for distinguishing between lymphoid and non-lymphoid crisis. More importantly, the blast cells of patients who eventually transform to lymphoid blast crisis may show CD10 and Ia positivity months before transformation occurs. The blast cells of non-lymphoid transformants do not show such positivity in the chronic phase [15; Roberts GT, unpublished observation.]

M7 constituted 6.7% of the transformations. The diagnosis was established largely on morphological grounds, based on both light and electron microscopy findings. The patients were older than those in the myeloid category, but similar in age to patients in the other categories.

Ten of 90 patients showed mixed lineage in blast crisis, a phenomenon that probably reflects the multipotent stem cell origin of CML [1]. The proportion of mixed-lineage blast cells in our series is in keeping with the findings described in previous reports [13,14,16]. This group includes only patients whose transformed blasts have maintained lineage consistency during observation. A number of other patients in the series demonstrated lineage switch while under treatment for blast crisis. This phenomenon is well recognized and can occur during antileukemia therapy [17]. Since lymphoblast crisis may respond more readily to chemotherapy, it may be important to determine the conditions and stimuli that promote one particular lineage.

In summary, we have observed 90 transformations among 248 patients (36.3%) with CML. This group of CML patients was younger than the ages usually reported from the West, an observation which may reflect the generally younger population in Saudi Arabia. The prevalence of Ph⁺ at diagnosis was similar to that reported elsewhere. The proportions of various blast cell phenotypes were similar to those reported from the West. Thus, apart from the younger age profile, Saudi Arabian patients with transformed CML possess similar characteristics to their Western counterparts.

Acknowledgments

The help of the following is gratefully acknowledged: Joyce Huebner, Haywood Pyle, Rosemary Elmes, and Gail Crawford for technical help; Linda Umali and Angie Palacio for preparing the manuscript.

References

1. Fialkow PJ, Jacobson RJ, Papayanopoulou T. Chronic myelocytic leukemia: clonal origin in a stem cell common to the granulocyte, erythrocyte, platelet and monocyte/macrophage. *Am J Med* 1977;63:125-30.
2. Rowley JD. A new consistent chromosomal abnormality in chronic myelogenous leukemia identified by quinacrine fluorescence and Giemsa staining. *Nature* 1973;143:290-1.
3. Moloney WC. Natural history of chronic granulocytic leukemia. *Clin Haematol* 1977;6:41-53.
4. Perreira L, Kearney L, Rassool F, et al. Correlation between chromosomal abnormalities and blast phenotype in the blast crisis of Ph-positive CGL. *Cancer Genet Cytogenet* 1986;22:29-34.
5. Diez-Martin J, Dewald GW, Pierre RV. Possible cytogenetic distinction between lymphoid and myeloid blast crisis in chronic granulocytic leukemia. *Am J Hematol* 1988;27:194-203.
6. Yunis JJ. New chromosome techniques in the study of human neoplasia. *Human Pathol* 1981;12:540-9.
7. Dacie JV, Lewis SM. *Practical haematology*, ed 6. Edinburgh: Churchill Livingstone, 1984.
8. Marie JP, Perrot JY, Boncheix C, et al. Determination of ultrastructural peroxidases and immunological membrane markers in the diagnosis of acute leukemias. *Blood* 1982;59:270-6.
9. Roberts GT, El-Badawi SB, Sackey K, et al. Lineage ambiguity in acute leukemia. *Cancer* 1986;58:1473-8.
10. Catovsky D. Ph⁺-positive acute leukemia and chronic granulocytic leukemia: one or two diseases? *Br J Haematol* 1979;42:493-8.
11. Rodenhuis S, Slater RM, Behrendt H, Veerman AJP. Distinguishing the Philadelphia chromosome of acute lymphoblastic leukemia from its counterpart in chronic myelogenous leukemia. *N Engl J Med* 1985;313:51-2.
12. Westbrook CA. The ABL oncogene in human leukemias. *Blood Rev* 1988;2:1-8.
13. Griffin JD, Todd KF, Ritz J, et al. Differentiation patterns in blastic phase of chronic myeloid leukemia. *Blood* 1983;61:85-91.
14. Fuscaldo KE, Brodsky I, Crilley P, Ligler FS. Cytogenetics and cell surface marker analysis in chronic myelocytic leukemia. II. Implications for patient management. *Cancer Genet Cytogenet* 1987;26:25-37.
15. Ligler FS, Brodsky I, Schlam MC, Fuscaldo KE. Cytogenetic and cell surface marker analysis in CML: I. prediction of phenotype of acute phase transformation. *Leuk Res* 1985;9:1093-8.
16. San Miguel JF, Tavares de Castro J, Matutes E, et al. Characterization of blast cells in chronic granulocytic leukemia in transformation, acute myelofibrosis and undifferentiated leukemia II studies with monoclonal antibodies and terminal transferase. *Br J Haematol* 1985;59:297-309.
17. Neame PB, Soamboosrup P, Browman G, et al. Simultaneous or sequential expression of lymphoid and myeloid phenotypes in acute leukemia. *Blood* 1985;65:142-8.

CURRENT PROCEDURES FOR BLADDER SUBSTITUTION AND URINARY DIVERSION AT KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE

Torsten Sundin, MD, PhD; Shahid Rafiq, FRCS;
Bo Johan Norlen, MD, PhD; Göran Alhgren, MD

في أعقاب استئصال جذري للمثانة بسبب السرطان أجريت عملية مفاغرة الأحليل الغشائي مع مثانة بديلة استحدثت بتغيير الشكل الأنبوبي لقطعة من القولون أو القولون واللفائفي لدى أربعة عشر (١٤) مريضاً وعملية تحويل البول إلى المستقيم بعد تقويته وتزويده بصمام لمريضتين. كانت الوفيات المبكرة معدومة ونسبة المضاعفات منخفضة، وكان متوسط فترة المتابعة هؤلاء المرضى ١٢ شهراً (٢ - ٢٨ شهراً)، ولم يعان أي مريض منهم من تدهور الوظيفة الكلوية أو خمج ظاهر في السبيل البولي خلال فترة المتابعة القصيرة هذه. كان تسعة مرضى من الذكور قادرين على احتجاز البول تماماً، وظهر بعض السلس أثناء النوم لدى أربعة، والسلس ليلاً ونهاراً لدى واحد. كان الانتصاب طبيعياً لدى أربعة منهم وضعيفاً لدى ثلاثة، وتلقى ثلاثة غرسة قضيبيية ولكن من المبكر جداً تقويم حاجة الآخرين لمثل هذه الغرسة. نجحت المريضتان في إحراز استمساك البول. وعليه يبدو أن التحويل البولي بدون مفاغرة أسلوب مأمون وموثوق، ويجب عرض أحد هذه البدائل الحديثة على المرضى الذين تجرى لهم عملية استئصال المثانة بسبب السرطان.

Following radical cystectomy for bladder cancer, 14 male patients had a detubularized colic or ileocolic bladder substitute anastomosed to the membranous urethra and two female patients had urinary diversion to the valved and augmented rectum. There were no early deaths and the complication rate was low. The patients were followed for a mean of 12 months (2-28 months). During this short-term follow-up, no patient suffered deterioration of renal function or symptomatic urinary tract infection. Of the male patients, nine were perfectly continent, four had some incontinence during sleep, and one patient was incontinent day and night. Four had normal erections and three weak erections. Three have received penile implants, but it is too early to assess the need for this in the others. The two female patients were continent. Continent urinary diversion without a stoma appears to be a safe and reliable procedure, and patients should be offered one of these newer alternatives for replacement of the urinary bladder after cystectomy for cancer.

During the first half of this century, ureterosigmoidostomy was the preferred method of urinary diversion. In 1950, Ferris and Odel [1] reported that nearly 80% of the patients in a large series

exhibited some degree of hyperchloremic acidosis after this procedure. At about the same time, Jacobs and Sterling [2] reported on a follow-up study initiated by the British Association of Urological Surgeons comprising more than 1600 patients. They found that about half of those who had not succumbed to their bladder cancer were dead of uremia within 5 years of the ureterosigmoidostomy.

Many of the problems of this procedure are related to the admixture of urine with the fecal stream

From the Urology Section, Department of Surgery, King Faisal Specialist Hospital and Research Centre, Riyadh.

Address reprint requests and correspondence to Dr. Sundin: Urology Section, Department of Surgery, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

Accepted for publication 13 June 1990.

and the ascendance of bacteria to the upper urinary tracts. Most urologists became weary of these complications. Thus, when Bricker [3], in 1950, popularized the use of an isolated ileal segment for cutaneous urinary diversion, this technique rapidly gained acceptance and has remained the standard approach to urinary diversion.

All newer forms of diversion aim at providing a continent urinary reservoir that can be emptied at intervals, either through spontaneous voiding or by intermittent self-catheterization. Freedom from a collecting appliance is psychologically important and improves the patient's quality of life. Another feature common to all newer diversion techniques is the construction of an antireflux mechanism. This may imply that the conservation of renal function will be comparable to that obtained by ileal conduit diversion, although the ultimate outcome of continent urinary diversion must await more years' experience for confirmation. However, in a recent study [4] it was found that the glomerular filtration rate was well preserved up to 10 years after the construction of a cecal reservoir for urine, and these results compared favorably with those for conduit urinary diversion. The aim of the present study was to present a short-term follow-up of 16 patients treated surgically using either of two procedures recently introduced for bladder substitution and continent urinary diversion, after radical cystectomy for bladder cancer.

Material and Methods

Fourteen male patients with a mean age of 44 years (range, 27–65 years) had undergone a radical cystectomy with removal of the bladder, prostate, and seminal vesicles. The nerve-sparing technique for radical prostatectomy described by Walsh et al [5] was used. All patients had bladder tumors in clinical stage T3, i.e., with deep muscle infiltration [T3a], and in most cases also with extravesical extension (T3b). Seven patients had squamous cell carcinoma; five, transitional cell carcinoma; and two, adenocarcinoma. Patients with transitional cell carcinoma underwent preoperative radiation therapy to a dose of 40 Gy during the 4 weeks preceding surgery, while the other patients had no radiotherapy. Formal pelvic lymphadenectomy was not performed. Nodes

macroscopically suspected of tumor involvement were removed. In cases with positive lymph nodes in frozen section as well as in other advanced cases where the prognosis was deemed poor, ureterosigmoidostomy was performed after cystectomy instead of bladder substitution.

Two different types of intestinal bladder substitutes were constructed and anastomosed to the membranous urethra. In the first three patients, the detubularized right colon was used (Figure 1A) [6], in the others a detubularized segment of the distal ileum, and the right colon was employed for bladder substitution (Figure 1B) [7].

Two female patients, aged 35 and 56 years, underwent preoperative radiation therapy for transitional cell carcinoma of the bladder followed by a radical cystectomy with removal of the bladder, urethra, anterior vaginal wall, uterus, ovaries, and salpinges. Urinary diversion was then performed to the augmented and valved rectum using the method of Kock et al (Figure 2) [8].

All patients had preoperative bowel preparation and a course of prophylactic antibiotics. The ureters were implanted into the bladder substitutes through submucous tunnels, and ureteric catheters (8F feeding tubes) were kept in place for 7 to 10 days. The substitutes, as well as the rectal pouches, were drained via a catheter for the 3 weeks following operation. The two female patients underwent a transverse colostomy which was closed after 2 to 3 months.

All operations were performed during 1987 through 1989. The mean follow-up time was 12 months (range, 2–28 months). All patients were seen at regular outpatient visits and during occasional readmissions for more thorough studies, including computed tomography and/or magnetic resonance imaging of the abdomen, voiding neocystourethrography, intravenous urography, renal isotope scan, urodynamics, and neocystoscopy, in addition to routine urine and blood tests.

Results

Mortality and Complications

There was no operative or postoperative mortality during the first hospital admission. One patient died of metastatic disease 14 months after the operation. The general condition of the other patients has remained satisfactory.

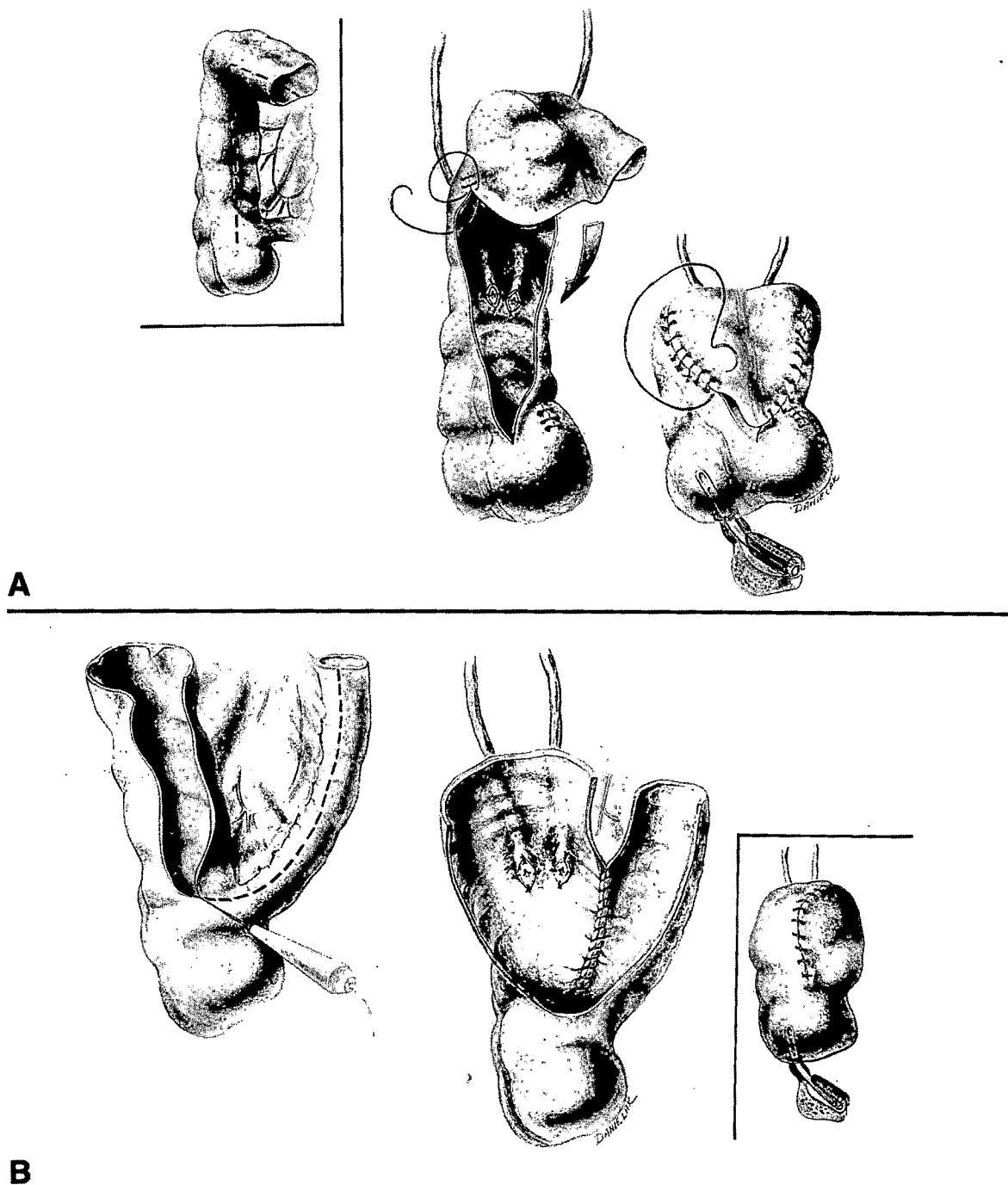


FIGURE 1. (A) Bladder substitute from a detubularized right colonic segment. The right colon is isolated on a pedicle (inset). The appendix and distal ileum are discarded. The colonic segment is opened along the anterior tenia, leaving the cecal pole intact. The ureters are implanted through submucous tunnels. The distal aspect of the opened colonic segment is folded over and the bladder substitute is closed. A urethrocecal anastomosis is performed over a urethral catheter. (B) Bladder substitute from a detubularized ileocolonic segment. After isolation of the segment, the right colon is opened along the anterior tenia, continuing along the antimesenteric border of ileum. Adjacent sides of ileum and colon are sutured together. The ureters are implanted into the colonic part of this patch, which is then folded over from side to side and closed (inset). The appendix is removed and a urethrocecal anastomosis performed. This anastomotic technique differs from that described by Light and Engelmann [7], who rotated the pouch 180 degrees and anastomosed the ileal moiety to the urethra.

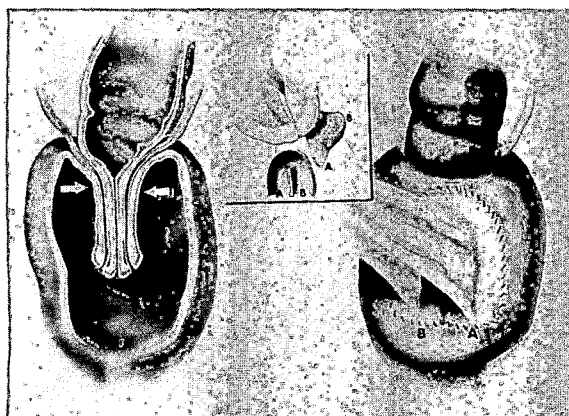


FIGURE 2. The augmented and valved rectum. The rectum is incised longitudinally in the anterior midline for 10 cm. A one-way intussusception valve is constructed in the rectosigmoid junction. The ureters are placed between the layers of the intussusception valve with mucosa-to-mucosa anastomoses between the intestine and ureters on the summit of the intussusception. A 20-cm-long split ileal segment is used as a U-shaped patch (inset) for augmentation by suturing it into the longitudinal opening in the anterior rectal wall.

One female patient who underwent the procedure for forming an augmented and valved rectal pouch required a laparotomy for intestinal obstruction by adhesions on the tenth postoperative day. Two male patients have had optical urethrotomy for anastomotic stricture between the substitute and the urethra. Otherwise, no operative revisions have been done.

Continence and Urodynamics

All 14 patients operated on with bladder substitution were found to have neobladder capacities of 200 to 700 ml, minimal residual urine of 0 to 10 ml, and acceptable flow rates of 10 to 37 ml/sec. Nine were continent day and night, including during sleep, and had low pressures (< 25 cm H_2O) in their substitutes on filling. Four patients were continent when awake but incontinent during sleep unless they woke themselves every 2 to 3 hours to go to the toilet. Three of them constituted the first patients operated on using a detubularized colonic substitute. Because of the incontinence and the finding of high maximum intraluminal pressures (40–55 cm H_2O), this type of substitute was abandoned in favor of the ileocolonic type. The fourth patient with incontinence during sleep also had high intraluminal pressure on filling (40 cm H_2O) despite having an

ileocolonic substitute. However, the urodynamic assessment was done only two months postoperatively, and from our experience, his condition may improve with the passage of time.

Finally, one male patient had stress incontinence when awake and was incontinent also during sleep. His urethral pressure profile maximum was only 28 cm H_2O , indicating sphincter weakness, while the maximum intraluminal pressure of the substitute was 30 cm H_2O .

Both female patients had low pressures (< 20 cm H_2O) on filling of their rectal pouches. One has been consistently continent, while the other, after 3 months' follow-up, complained of some incontinence for fluids during sleep. She is now treated with an alpha-adrenoceptor agonist (phenylpropanolamine, 5 mg t.i.d. orally) and is perfectly continent.

Potency

Four men have had postoperative erections and normal sexual potency. Three others claim that they have erections, but not sufficient enough for intercourse. Three patients have had implantation of a penile prosthesis, while the remaining patients were either not interested in having an implant or it was too soon after the operation to allow for definitive evaluation of their potency.

Metabolic Disturbances

Two male patients with preoperative ureteric obstruction and renal failure have had postoperative acidosis. In one the serum creatinine level has still been high at 200 $\mu\text{mol/L}$ and the patient requires sodium bicarbonate for treatment of the acidosis. The other patient now has a normal serum creatinine level and only a slight acidosis, and is not being treated. All other patients, including the two female patients with a rectal pouch, have had normal metabolic values.

Bacteriology

Clinical urinary tract infection has not been a problem. However, repeated cultures of urine obtained from the substitutes demonstrated significant growth in about half of the cases. Thus, almost all patients had positive urinary culture on some occasion, but asymptomatic bacteriuria has not been treated.

The two female patients with rectal pouches





FIGURE 3. (A) Contrast filling of augmented and valved rectal pouch via a catheter through anus (Note: No reflux to ureters or sigmoid.) (B) Antegrade contrast filling of the sigmoid and rectal pouch from the transverse colostomy two months postoperatively. (Note: unobstructed passage through one-way intussusception valve, recognizable by rows of metal staples.)

and fecal admixture of their urine have not shown clinical signs of urinary tract infection.

Upper Urinary Tract Dilatation and Reflux

The width of the upper urinary tracts has been unchanged or less dilated than was the case preoperatively in all patients. No reflux to the upper urinary tracts has been demonstrated in any patient, either from the bladder substitutes or from the rectal pouches.

Discussion

The description of ureterosigmoidostomy in the introduction is more historical than factual, because the availability of antibiotics and institution of continuous treatment of electrolyte disturbances have changed the outlook. In a patient with rectal continence, who is free of renal disease and does not have ureteric dilatation, ureterosigmoidostomy can be expected to be successful. However, besides ascending urinary tract infection and electrolyte disturbances, there is a definite risk that in time an adenocarcinoma may develop at the junction of ureter and bowel [9]. In old patients, as well as in other patients with the expectancy of short survival (e.g., after salvage cystectomy), we still prefer ureterosigmoidostomy because of its relative simplicity. Experience from this institution [10] appears to support this policy.

We find that conduit diversion with an external collecting device is less well tolerated in patients here than in those from Western countries. Patients will occasionally not consent to cystectomy out of fear of this type of diversion. It may be that the aesthetic image of one's own body is psychologically more important in this part of the world. For this reason we have stopped performing cutaneous conduit diversions after cystectomy for cancer. However, such diversion may still be the best alternative in some neuropathic cases.

The electrolyte disturbances so common in patients with ureterosigmoidostomy did not generally occur after bladder substitution in our patients. The reason for this seems to be that, although the urine is in contact with the bowel for a longer time than is the case in conduit diversion, the absorptive surface area is smaller than that when the ureters are implanted into the intact

colon. Furthermore, all our patients with intact renal function have no electrolyte disturbances, implying an inherent ability of the kidneys to handle an added electrolyte insult [11]. In two of our patients with preoperative ureteric obstruction, mild acidosis persisted or was slightly accentuated after construction of an intestinal bladder substitute.

Regarding the functional characteristics of the bladder substitutes, the fact that intact intestinal loops, no matter if derived from small or large bowel, produce high-pressure peristaltic contractions if used as a bladder substitute was first proven urodynamically by Ekman et al [12] in 1965. Detubularization (i.e., folding of the split intestine into a more spherical form) was demonstrated to be an effective way to create a low-pressure bladder substitute [12].

In the present series, the capacity of the bladder substitutes varied from 200 to 700 ml and was thus sufficient for storage of the urine produced during several hours. Nevertheless, some of the patients experienced nighttime incontinence. This was the case in all three patients with substitutes formed from the detubularized right colon. Urodynamic investigations demonstrated that pressure waves occurred with filling of those substitutes which were higher than the pressure waves in cases where the ileum and right colon constituted the detubularized reservoir. It seems that, when awake, the patient is conscious of these pressure waves and remains continent by means of voluntary external sphincter contraction, which can be maintained during the short period of reservoir contraction. He then empties his substitute bladder by straining and relaxation of the pelvic floor. However, during sleep these contraction waves may overcome the resistance of the passive continence mechanism, causing incontinence. Only reservoirs with a pressure rise lower than that exerted by this passive continence mechanism seem to ensure continence during sleep. An alternative explanation for incontinence only during sleep could be that the passive urethral closure mechanism is more effective in the awake state, and ensures continence without the contribution of voluntary sphincter contraction.

One patient had incontinence during sleep and stress incontinence during the day. Urodynamic investigations showed pressure waves not exceed-

ing 30 cm H₂O in his ileocolonic reservoir, but the urethral pressure profile was low (maximum, 28 cm H₂O). His incontinence was evidently secondary to a poor distal sphincteric mechanism, possibly caused by optical urethrotomy for an anastomotic stricture. He has been offered an artificial urinary sphincter implantation, but so far has declined and wears a condom appliance.

It seems likely that the nerve-sparing technique of Walsh et al [5] is important, not only for preserving sexual function but also for postoperative passive continence. The neurovascular bundles running on each side of the prostate contain pelvic nerve fibers essential for erection. However, the studies of Gosling et al indicate that the pelvic nerves contain somatic fibers [13] innervating the part of the rhabdosphincter with slow-twitch fibers suitable for passive continence [14].

The sexual potency in our patients following the nerve-sparing technique was similar to that described in some reports after radical prostatectomy [15,16], but did not reach the 70% reported by Eggleston and Walsh in 1985 [17]. The relatively young age in our patients should be conducive to good potency, but the extravesical tumor growth necessitating sacrifice of one neurovascular bundle in some of our patients endangered the preservation of erection [16].

Kock et al [8] recently described a novel procedure for urinary diversion (Figure 2). We have so far used the procedure in two female patients after radical cystectomy for bladder cancer. This method would also be a suitable alternative in male patients when a total urethrectomy is necessary, such as in cases where there is tumor involvement of the urethra or when biopsy shows carcinoma in situ of the urethra.

The rationale of the augmented and valved rectum is as follows. To lessen the risk of electrolyte disturbances, the absorptive mucosal area is limited to a rectal reservoir by means of a one-way intussusception valve constructed in the rectosigmoid junction which prevents urine refluxing into the sigmoid colon, while at the same time allowing an unobstructed passage of the fecal stream (Figure 3). Thus, there have been no complaints about bowel function from either of our two female patients. To protect the upper urinary tracts from reflux of reservoir contents, the ureters are placed between the layers of the intestinal

intussusception valve, with mucosa-to-mucosa anastomoses between the intestine and ureters on the summit of the intussusception. Finally, anal continence is enhanced by augmentation of the rectum through the use of a U-shaped patch of a 20-cm-long split ileal segment. This gives a large-capacity, low-pressure reservoir. Our two patients have experienced perfect anal continence, even though one of them so far requires alpha-adrenoceptor stimulation to produce contraction of her anal muscles. No reflux of contrast was demonstrated, either to the upper urinary tracts or to the sigmoid colon, when the reservoir was filled with contrast via the anus (Figure 3A). One drawback of this method might be the eventual cancer formation at the ureterointestinal junction. Experimentally the malignant changes do not occur if the feces are immediately excluded from the suture line through use of a proximal colostomy [9]. Furthermore, initial proximal colostomy, followed by closure of the colostomy after 1 to 3 months, as in the clinical diversion method, seemed experimentally to ensure relative protection from tumor formation [9].

An alternative to this method for use after cystectomy with total urethrectomy is continent cutaneous diversion, e.g., the Kock pouch [18] or the cecal reservoir [19], which are emptied intermittently by means of self-catheterization. Although continence is achieved, the presence of an abdominal stoma and the potential problems with intermittent catheterization seem less appealing when compared with the possibility of avoiding any stoma.

References

1. Ferris DO, Odel HM. Electrolyte pattern of the blood after bilateral ureterosigmoidostomy. *JAMA* 1950;142:634-41.
2. Jacobs A, Sterling WB. The late results of ureterocolic anastomosis. *Br J Urol* 1952;24:259-316.
3. Bricker EM. Bladder substitution after pelvic evisceration. *Surg Gynecol Obstet* 1950;30:1511-21.
4. Månsson W, Ahlgren G, White T. Glomerular filtration rate up to 10 years after urinary diversion of different types. *Scand J Urol Nephrol* 1989;23:195-200.
5. Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. *Prostate* 1983;4:473-85.
6. Goldwasser B, Barrett DM, Benson RC Jr. Bladder replacement with use of a detubularized right colonic segment: preliminary report of a new technique. *Mayo Clin Proc* 1986;61:615-21.

7. Light JK, Engelmann UH. Le bag: total replacement of the bladder using an ileocolonic pouch. *J Urol* 1986;136:27-31.
8. Kock NG, Ghoneim MA, Lycke KG, Mahran MR. Urinary diversion to the augmented and valved rectum: preliminary results with a novel surgical procedure. *J Urol* 1988;140:1375-9.
9. Gittes RB. Carcinogenesis in ureterosigmoidostomy. *Urol Clin North Am* 1986;13:201-5.
10. Bissada NK, Morcos RR, Hanash KA, et al. Ureterosigmoidostomy revisited. *J Urol* 1986;135(4 part 2):370A.
11. Kosko JW, Kursh ED, Resnick MI. Metabolic complications of urologic intestinal substitutes. *Urol Clin North Am* 1986;13:193-200.
12. Ekman H, Jacobsson B, Kock NG, Sundin T. The functional behaviour of different types of intestinal urinary bladder substitutes. XIII Congr de la Soc Int d' Urol 1965;2:213-7.
13. Gosling JA, Chilton CP. The anatomy of the bladder, urethra and pelvic floor. In: Mundy AR, Stephenson TP, Wein AJ, eds. *Urodynamics; principles, practice and application*. Edinburgh: Churchill, Livingstone, 1984;3-13.
14. Gosling JA, Dixon JS, Critchley HOD, Thompson S-A. A comparative study of the human external sphincter and periurethral levator ani muscles. *Br J Urol* 1981;53:35-41.
15. Catalona WJ, Dresner SM. Nerve-sparing radical prostatectomy: extra-prostatic tumor extension and preservation of erectile function. *J Urol* 1985;134:1149-51.
16. Ritchie AWS, James K, de Kernion JB. Early post-operative morbidity of total prostatectomy. *Br J Urol* 1989;64:511-5.
17. Eggleston JC, Walsh PC. Radical prostatectomy with preservation of sexual function: pathological findings in the first 100 cases. *J Urol* 1985;134:1146-8.
18. Kock NG, Nilsson AE, Nilsson LO, et al. Urinary diversion in a continent ileal reservoir: clinical results in 12 patients. *J Urol* 1982;128:469-75.
19. Mansson W, Colleen S, Sundin T. The continent caecal reservoir for urinary diversion. *World J Urol* 1985;3:173-8.

PATTERN OF CANCER AT ASIR CENTRAL HOSPITAL, ABHA, SAUDI ARABIA

Abdur Rauf Khan, MD, FCAP; Nazir K. Hussain, MD, FCAP;
Abdulaziz Al-Saigh, FRCSI; Tarek Malatani, FRCS(C);
Anwar A. Sheikha, MBChB, MRCPPath, FCAP, FRCPA

تمت على مدى ثلاث سنوات، ١٩٨٧م - ١٩٨٩م، معاينة ستمائة وسبع وتسعين حالة سرطان مؤكدة بالفحص النسيجي وذلك في مستشفى عسير المركزي في أبها بالمملكة العربية السعودية. وقد حددت نسب تواتر السرطان (نسبية وتقريبية) في مواضع مختلفة من الجسم. وكانت أكثر المواضع تواتراً بين الذكور هي الجلد والكبد والنسيج اللمفاوي (أي الأورام اللمفية غير اللمفاوية) والثثانة، الدم (ابيضاضات الدم) والمعدة والقولون والمريء والجهاز العصبي المركزي والموتة. وكان سرطان الجلد أيضاً أكثر الأنواع تواتراً بين الإناث، يليه سرطان الثدي والنسيج اللمفاوي (الأورام اللمفاوية غير اللمفاوية) والدم (ابيضاضات الدم) والدرقية والمعدة والقولون وجوف الفم والمريء وعنق الرحم.

Six hundred ninety-seven histologically confirmed cases of cancer were seen in the three-year period, 1987 to 1989, at Asir Central Hospital in Abha, Saudi Arabia. Percentage (crude relative) frequencies of cancer at various sites were determined. The most common cancer sites among males were skin, liver, lymphoid tissue (i.e., non-Hodgkin's lymphomas), bladder, blood (leukemias), stomach, colon, esophagus, central nervous system, and prostate. Skin cancer was also the most common cancer among females, followed by the breast, lymphoid tissue (non-Hodgkin's lymphomas), blood (leukemias), thyroid, stomach, colon, oral cavity, esophagus, and cervix.

There is currently no national cancer registry in Saudi Arabia [1]; therefore, the incidence and mortality statistics for cancer cannot be determined accurately. Reports regarding the incidence of cancer originating from the eastern [2], central [3-5], western [6], and Al-Baha [7] regions of Saudi Arabia were derived from hospital statistics. No separate figures concerning the pattern of malignancies in the Asir region are currently available. Based on histologically confirmed diagnoses, our study attempts to delineate the pattern of malignancies for the Asir region.

The Asir region (Figure 1) has a high population density. About 75% of the inhabitants live in rural areas and are engaged in agriculture, trade, or government work. There is less involvement in fishing and animal husbandry [8]. Asir Central Hospital (ACH), in Abha, is a 576-bed, regional referral facility for patients of the Asir region. The surgical pathology laboratory of ACH also furnishes routine services to other hospitals located in Khamis Mushait, Bisha, Zahran-al-Janoob, Sarat Abidah, Ahad Rufidah, Rijal Alma, and Muhayl.

Material and Methods

From January 1987 to December 1989 the surgical pathology laboratory at ACH received 18,174 surgical and biopsy specimens. The histopathology reports of the specimens were reviewed and those containing a diagnosis of malignancy were

From the Departments of Pathology (Drs. Khan and Sheikha), Surgery (Drs. Al-Saigh and Malatani), College of Medicine, King Saud University, and Asir Central Hospital (Dr. Hussain), Abha.

Address reprint requests and correspondence to Dr. Khan: Department of Pathology, College of Medicine, King Saud University, P.O. Box 641, Abha, Saudi Arabia.

Accepted for publication 12 June 1990.



FIGURE 1. Map of Saudi Arabia, showing the location of the Asir Province.

collected. Only one pathology report per patient was included in our data, even though multiple specimens may have been examined. Malignancies were then tabulated according to the organs or affected primary body sites. Uncommon tumors of sites such as lung, bone, nasopharynx, uterus, ovary, testis, salivary glands, adrenals, gallbladder, soft tissue, pancreas, thymus, paraganglia, and maxillary antrum were designated as "others." The sex and nationality of patients in each category were also identified. The nationality for some patients was unknown. To facilitate a comparison of malignancies in each category with previously published data [2-7], percentage (crude relative) frequencies were determined.

Results

During the three-year period, 1987 to 1989, 697 cases of histologically confirmed malignancies were seen (Tables 1 to 3). The most common malignancy in males was skin cancer, representing 14.6% of the cases, and then in descending frequency come cancers of the liver, lymphoid tissue (i.e., non-Hodgkin's lymphomas), bladder, blood (leukemias), stomach, colon, esophagus, central nervous system, and prostate. Skin cancer was also the most common malignancy in females, occurring in 12.5%, followed by cancer of the breast, lymphoid tissue (i.e., non-Hodgkin's lym-

phomas), blood (leukemias), thyroid, stomach, colon, oral cavity, esophagus, and cervix. Other tumors constituted 24.9% of the cases in males and 35.2% of the cases in females.

Discussion

In our study, skin cancer was the most common malignancy in both males and females (14.6% and 12.5%, respectively). Our findings were consistent with the observation of Willen and Patterson [7] and Stirling et al [6]. In the Willen and Pat-

TABLE 1. Rank order and percentage frequencies of malignant neoplasms at Asir Central Hospital in 425 males.

Rank order	Site of malignancy	No. (%)
1	Skin	62(14.6)
2	Liver	47(11.0)
3	Non-Hodgkin's lymphoma	41(9.6)
4	Bladder	40(9.4)
5	Leukemia	38(8.9)
6	Stomach	34(8.0)
7	Colon	20(4.7)
8	Esophagus	16(3.8)
9	Central nervous system	11(2.6)
10	Prostate	10(2.3)
11	Others ^a	106(24.9)

^aThis category constitutes uncommon tumors of sites such as the lung, bone, nasopharynx, testis, salivary glands, adrenals, gallbladder, soft tissue, pancreas, thymus, paraganglia, and maxillary antrum.

TABLE 2. Rank order and percentage frequencies of malignant neoplasms at Asir Central Hospital in 272 females.

Rank order	Site of malignancy	No. (%)
1	Skin	34(12.5)
2	Breast	25(9.2)
3	Non-Hodgkin's lymphoma	23(8.4)
4	Leukemia	20(7.3)
5	Thyroid	17(6.3)
6	Stomach	13(4.8)
7	Colon	13(4.8)
8	Oral	11(4.0)
9	Esophagus	10(3.7)
10	Cervix	10(3.7)
11	Others ^a	96(35.2)

^aSee Table 1 for explanation of this category.

TABLE 3. *Malignant neoplasms in Saudi citizens and other nationals at Asir Central Hospital.*

Rank order	Site of malignancy	Saudi	Others	Not specified	Total
1	Skin	78	8	10	96
2	Non-Hodgkin's lymphoma	49	4	11	64
3	Leukemia	49	7	2	58
4	Liver	45	3	6	54
5	Stomach	35	8	4	47
6	Bladder	25	11	9	45
7	Colon	24	3	6	33
8	Esophagus	21	4	1	26
9	Breast	15	9	1	25
10	Thyroid	15	2	4	21
11	Oral	11	4	5	20
12	Central nervous system	16	1	1	18
13	Lung	12	2	0	14
14	Prostate	9	1	0	10
15	Cervix	9	1	0	10
16	Others	112	25	19	156

tersson study of 659 cases of cancers from Al-Baha region of Saudi Arabia, the incidence of skin cancer was 15.2% in males and 14.2% in females. Stirling et al reported a high proportion of skin cancer (15.5%) among 1000 consecutive cases of malignant neoplasm in Saudi residents of the western region of Saudi Arabia. Our findings, however, differ from the observations of El-Akkad et al [3] who reported a low rate of skin cancer at King Faisal Specialist Hospital and Research Centre, Riyadh (KFSH&RC), a main referral center for cancer patients from all areas of Saudi Arabia. Many different factors influence the referral to this center. Most skin cancers are not life threatening and are therefore not referred. Moreover, the discrepancy of skin cancers among the various series probably depends on whether the series consists of clinical (KFSH&RC) or pathological (present series) material, the latter usually manifesting a much higher relative frequency of skin cancer. Rabadi [2] even excluded skin cancers (except melanomas) from his analysis of all cases of malignancy seen at Dhahran Health Center because of the trivial nature of such malignancies.

In the present study, primary hepatocellular

carcinoma (PHC) ranked second in frequency in males and accounted for 11% of all malignancies in males. PHC is a commonly observed malignancy in Saudi Arabia, although its incidence varies according to the time and place of reporting [9]. Our data showed a higher frequency of PHC in the Asir region (11%) as compared with Al-Baha (6.5%) [7], Riyadh (5%) [3], and Dhahran (3.3%) [2]. Evidence suggests that hepatitis B virus and schistosomiasis are important factors in the pathogenesis of PHC [10,11] and are common afflictions among the residents of the Asir region [12,13].

In our study, breast cancer was the second most common malignancy in females. A similar high incidence of breast cancer has been reported from Al-Baha [7], Dhahran [2], and Riyadh [3]. The frequencies of gastric carcinomas, lymphomas, and leukemias in the Asir region were similar to those reported from Dhahran [2], Riyadh [3], and Al-Baha [7].

Cancers of the bladder and oral cavity deserve special mention. In our study, bladder cancer was the fourth most common malignancy in males (9.4%). Our results agree with the findings of El-Akkad et al [3], who reported that the crude relative frequency of bladder cancer in the southwestern region of Saudi Arabia was roughly double that of the rest of the country (6.0% versus 3.7% in males and 2.4% versus 1.1% in females). A high incidence of bladder cancer has also been reported from the Al-Baha [7] region (7.1% in males). The Asir region is a predominantly mountainous area with a generally cool and less arid climate than that found elsewhere in the Kingdom. Because of the widespread practice of traditional agriculture, schistosomiasis is common in the Asir region [9], and this disease is considered a contributing factor in the development of bladder cancer [14].

El-Akkad et al [3], at KFSH&RC, observed that the crude relative frequency of oral cancer for females (12.9%) from the southwestern region of Saudi Arabia was three times that for the country as a whole (4.4%), and in males it was twice as high (8.2% versus 4.1%) [3]. The authors attributed this finding to the chewing of *Shamma*, which is a mixture of tobacco, slaked lime, black pepper, oils, flavoring, and other ingredients. In contrast, our preliminary findings revealed a low

incidence of oral cancer in the Asir region (2.1% in males and 4.0% in females). The difference may be because El-Akkad et al [3] included the Jizan area in their report, while we limited our population to that of the Asir region. In a study conducted by Amer et al [15], 33 of 68 patients with oral cancer referred to KFSH&RC admitted using *Shamma*. Of these users, 85% were referred from the Southern province, particularly from the Jizan area (73%). A further study that concentrates on the Jizan area would more accurately depict the true incidence of oral cancer in that area. Additionally, because the use of *Shamma* has been barred since 1983 [9], a decline in the incidence of oral cancer should be expected.

Colorectal cancer occurs at varying frequencies in the populace of different areas of the world. It is the second most common cancer in the United States [16]. Preliminary findings from several investigators [3,4,17-19], as well as our data, have implied that carcinoma of the rectum and large bowel is not as common in the residents of Saudi Arabia as it is for those of Western Europe and North America.

Acknowledgment

We gratefully acknowledge the help of Dr. Raymond A. Bobo and Ms. Nishath Hussain, who critically reviewed this paper and provided invaluable suggestions. Acknowledgment is also accorded to Messrs. Eric Avila and Gil C. Alpas for preparing the manuscript and for technical assistance.

References

1. Amer MH. The need for a national cancer registry in Saudi Arabia. *Ann Saudi Med* 1987;7(4):263-4.
2. Rabadi SJ. Cancer at Dhahran Health Center, Saudi Arabia. *Ann Saudi Med* 1987;7(4):288-93.
3. El-Akkad SM, Amer MH, Lin GS, et al. Pattern of cancer in Saudi Arabs referred to King Faisal Specialist Hospital. *Cancer* 1986;58:1172-8.
4. Amer MH. Pattern of cancer in Saudi Arabia: a personal experience based on the management of 1000 patients—Part 1. *King Faisal Specialist Hosp Med J* 1982;2(4):203-15.
5. Koreich OM, Al-Kuhaymi R. Cancer in Saudi Arabia: Riyadh Al-Kharj Hospital Programme experience. *Saudi Med J* 1984;5:217-23.
6. Stirling G, Khalil AM, Nada GN, et al. Malignant neoplasms in Saudi Arabia. *Cancer* 1979;1(2):89-94.
7. Willen R, Pattersson BA. Pattern of malignant tumours in King Fahad Hospital, Al-Baha, Saudi Arabia. *Saudi Med J* 1989;10(6):498-502.
8. Sebai ZA. A new faculty of medicine at Abha, Saudi Arabia. *Saudi Med J* 1983;4(1):77-82.
9. Sebai ZA. Cancer in Saudi Arabia. *Ann Saudi Med* 1989;9(1):55-63.
10. Ashraf SJ, Arya SC, El-Sayed M, et al. A profile of primary hepatocellular carcinoma patients in the Gizan area of Saudi Arabia. *Cancer* 1986;58:2163-8.
11. Inaba Y, Maruchi N, Matsuda M, et al. A case-control study on liver cancer with special emphasis on the possible aetiological role of schistosomiasis. *Int J Epidemiol* 1984;13:408-12.
12. Al-Faleh FZ. Hepatitis B infection in Saudi Arabia. *Ann Saudi Med* 1988;8(6):474-80.
13. Cutajar CL. Urinary schistosomiasis in Saudi Arabia. *Saudi Med J* 1983;4:67-76.
14. Mee AD. Aetiological aspects of bladder cancer in urinary bilharzia. *Saudi Med J* 1982;3:123-8.
15. Amer M, Bull CA, Daouk MN, et al. *Shamma* usage and oral cancer in Saudi Arabia. *Ann Saudi Med* 1985;5(3):135-40.
16. Robbins SL, Cotran RS, Kumar V. *Pathologic basis of disease*. Philadelphia: Saunders, 1984:869.
17. Bedikian AY, Bakhsh K, de Niord R, et al. Colorectal carcinoma during the first four decades of life. *Ann Saudi Med* 1987;7(4):282-7.
18. Mohamed ARE, Al-Karawi MA, Koreich OM. Incidence of colorectal cancer and colonic polyps in Saudi patients. *Ann Saudi Med* 1990;10(1):19-21.
19. Borghol M, de Niord RN. Carcinoma of the rectum at King Faisal Specialist Hospital: a four-year retrospective review. *Ann Saudi Med* 1990;10(1):22-8.

HYPERCALCEMIA IN ACTIVE PULMONARY TUBERCULOSIS

Sulaiman A. Al-Majed, FRCP(C), FCCP;
 Riad Sulimani, FRCP(C), FACP; Faisal Al-Kassimi, MRCP, FCCP;
 Lalit Pandya, MSc, MD, MRCP; Sameer Huraib, FRCP(C);
 Nasser Al-Sharif, MD, DTM

أجريت دراسة استطلاعية على ٢٤١ مريضاً يعانون من سل الرئة النشط، وتبين أن ٦٢ مريضاً منهم (٢٦٪) يعانون من فرط الكلسمية. تم اكتشاف فرط الكلسمية عند المراجعة في ٤٨ مريضاً وظاهر لدى ١٤ مريضاً بعد فترة ٤ - ٦ أسابيع من العلاج الكيميائي المضاد للتدرن. كان متوسط معدل الكالسيوم المصلي في هذه الحالات ($\pm$ انحراف معياري) ٢,٧٨ (± 0.137), ١٣٧ (± 0.137) مايكرومول/لتر. كان ارتفاع معدل الكالسيوم طفيفاً في معظم الحالات (٦٦,٧٪) إذ بقي أدنى من ٢,٨ مايكرومول/لتر وتراوح في ٣٥٪ من الحالات بين ٢,٨ و ٣,٠ مايكرومول/لتر. ووصل إلى ٣,٠ مايكرومول/لتر في ٢,٤٪ فقط من الحالات، وقد يفسر هذا غياب الأعراض المرتبطة بفرط الكلسمية. كان فرط الكلسمية أكثر تواتراً في المرضى الذين تتجاوز أعمارهم ٥٠ عاماً ($P < 0.05$) لكنه لم يترابط مع شدة انتشار السل مقدراً بالمظهر الشعاعي. حدثت العودة إلى الكلسمية الطبيعية تلقائياً في جميع المرضى الإثني والأربعين الذين أجريت لهم سلسلة من الاستقصاءات على تركيز الكالسيوم المصلي بعد ٦ إلى ٨ أسابيع من العلاج الكيميائي. من المعلوم أن المملكة العربية السعودية ينتشر فيها عوز فيتامين (د) بدرجة كبيرة ولم يكن أحد من مرضانا قعيد الفراش ولا تلقى أي منهم جرعات مساندة من فيتامين (د) أو الفيتامينات المتعددة. يؤيد هذا فكرة أن تناول فيتامين (د) لا يلعب دوراً رئيسياً في تحريض فرط الكلسمية في حالات سل الرئة النشط، خلافاً للاشتباه القديم بذلك.

In a retrospective review of 241 patients with active pulmonary tuberculosis, hypercalcemia was found in 62 (26%). It was detected on presentation in 48 patients and developed in 14 patients 4 to 6 weeks after the start of antituberculous chemotherapy. The mean ($\pm$ SD) serum calcium level in those cases was 2.78 (± 0.137) mmol/L. The majority of cases (67.6%) had a mild rise in the calcium level that remained below 2.8 mmol/L but 35% had a level that ranged between 2.8 and 3.0 mmol/L. Only 2.4% had serum level higher than 3.0 mmol/L, which could explain the predominant absence of hypercalcemia-related symptoms. Hypercalcemia was more common in patients older than 50 years ($P < 0.05$), but this did not correlate with the extent of the tuberculosis shown on radiological evaluation. Spontaneous return to normocalcemia occurred in all 42 patients who underwent serial assessments of their serum calcium concentration, 6 to 8 weeks after the start of chemotherapy. Saudi Arabia is known

From the Division of Respiratory Medicine (Drs. Al-Majed), Division of Endocrinology (Dr. Sulimani), and Division of Nephrology (Dr. Huraib), King Khalid University Hospital, and Sahary Chest Hospital (Drs. Pandya, Al-Sharif), Riyadh.

Address reprint requests and correspondence to Dr. Al-Majed: Department of Medicine, Division of Respiratory Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Accepted for publication 12 June 1990.

to have a high prevalence of vitamin D deficiency, but none of our patients were immobilized or had received vitamin D supplements or multivitamins. This supports the view that vitamin D intake does not play a major role in inducing hypercalcemia in cases of active pulmonary tuberculosis, as has been suspected.

Hypercalcemia has been reported to occur in conjunction with various granulomatous diseases, such as tuberculosis [1-5], sarcoidosis [6], disseminated fungal infection [7,8], and berylliosis [9]. However, some studies failed to detect any significant hypercalcemia associated with tuberculosis [10-12]. As in sarcoidosis, hypersensitivity to vitamin D was considered the likely mechanism for hypercalcemia in tuberculosis [13], and some studies documented the occurrence of hypercalcemia in patients given vitamin D supplements [14].

Although Saudi Arabia is a sunny country, vitamin D deficiency is common [15] and is attributed to dietary habits and an actual lack of exposure to the sun. The present study was therefore designed to analyze retrospectively the effects of tuberculosis on calcium homeostasis in this environment, and to discover whether a correlation existed between the presence of hypercalcemia and patient age, as well as between the extent and severity of the disease.

Patients and Methods

We retrospectively reviewed the records of 241 patients with smear- and culture-positive pulmonary tuberculosis. All patients had been seen at the Chest Hospital and King Khalid University Hospital, Riyadh, between July 1986 and October 1989. None of the patients were on diuretics, vitamin D, or calcium supplements or suffered from renal failure; all were fully ambulatory. Bed-ridden or immobilized patients were excluded. All patients were followed clinically for a minimum of 9 months. The extent of tuberculosis on admission was determined radiologically, using the classification of the National Tuberculosis Association of the USA [16], and graded as advanced, moderate, or minimal.

In addition, the following information was recorded: antituberculous drugs given, and values noted for serum urea, creatinine and electrolytes, serum albumin, alkaline phosphatase, serum calcium, and phosphate, before and during

chemotherapy. A tourniquet was used to draw blood in all cases. The serum calcium value was corrected to the serum albumin value using the formula described by Kleeman et al [17]. This was done to compensate for the mild increase in calcium level which can result from tourniquet application, as venous stasis is known to falsely raise the serum calcium level due to a hemoconcentration of albumin [18]. Hypercalcemia was defined as a serum calcium level higher than 2.6 mmol/L, which is the upper limit of normal for Saudis [19,20].

Results

Table 1 gives the age and sex characteristics of the normocalcemic and hypercalcemic groups. We studied a total of 241 patients, of whom 148 were males and 93, females. Sixty-two patients (26%) had a calcium level higher than 2.6 mmol/L, though other biochemical variables were normal. There were 40 males and 22 females with an age of 6 to 80 years. Hypercalcemia was detected on presentation in 48 patients, but in 14 others developed 4 to 6 weeks after starting antituberculous chemotherapy. The mean ($\pm$ SD) serum calcium concentration in those cases was 2.78 ($\pm$ 0.137) mmol/L. The majority of cases (67.6%) had a mild rise in the serum calcium level below 2.8 mmol/L; in 35% the level was below 3.0 mmol/L. Only 2.4% had a serum calcium level higher than 3.0 mmol/L. None of the patients had symptoms attributable to hypercalcemia.

For analysis purposes, the patients were divided

TABLE 1. Sex and age characteristics of the patients.

Patient characteristics	No. of patients	No. of patients with hypercalcemia
Male	148(61.4%)	40(65%) ^a
Female	93(38.6%)	22(35%)
Age range (yr)	6-90	6-80
Mean age $\pm$ SD (yr)	36 $\pm$ 16.91	38 $\pm$ 18.2

^aPercentage of the total number of patients.

into two main groups: those who were below the age of 50 and those above. Hypercalcemia was found in 47 of the 203 (23%) patients younger than 50 years, compared with 15 to 38 (39%) 50 years and older, and the difference was significant at $P < 0.05$. Twelve of the 36 (33%) patients with advanced disease had hypercalcemia, whereas 50 of 205 (24%) patients with moderate or mild disease had hypercalcemia, though the difference between the two groups was not significant at $P > 0.05$.

Of the 62 patients with hypercalcemia, 42 underwent serial estimations of serum calcium, which reverted to normal within 6 to 8 weeks following the start of chemotherapy.

Discussion

We found a 26% prevalence of hypercalcemia in patients with active pulmonary tuberculosis. This agrees with observations from previous studies of between 26 and 48% [5,14,21]. The resolution of hypercalcemia after institution of tuberculous chemotherapy in our patients makes unlikely other causes of hypercalcemia, such as the application of a tourniquet or existence of malignancy. Also, all patients were followed for 9 months, and during that time showed no clinical evidence of malignancy. Hyperparathyroidism, which occurs in 1 to 6.2 per thousand in the general population [22], could not account for the high prevalence recorded in our study. A survey by the British Thoracic Society [12] found no hypercalcemia in a group of 287 patients with active tuberculosis. Other workers have also failed to detect any hypercalcemia at the time of diagnosis of tuberculosis [10,11]. The discrepancy between various studies is difficult to explain, but may represent differences in calcium intake in the diet as well as differences in the population studied. Similar to the findings of Kitrou et al [20], we found hypercalcemia was significantly more frequent in subjects older than 50 years ($P < 0.05$). This could not be attributed to an effect resulting from immobilization, as all our patients were fully ambulatory. Although there was a trend for a correlation between the radiological extent of tuberculosis and the presence of hypercalcemia, the trend was not statistically significant ($P > 0.05$). This agrees with the findings of previous studies [5,21,23].

Hypercalcemia was documented at presentation in 48 of our patients, but appeared only 4 to 6 weeks after the start of chemotherapy in another 14. This finding militates against Ketrou et al's [20] view that hypercalcemia is triggered by anti-tuberculosis chemotherapy. The hypercalcemia appears to be influenced in some way by the tuberculosis, as it cleared with the continuation of chemotherapy.

The lack of symptoms of hypercalcemia in our study and others [5,14] reflects the predominantly mild rise of serum calcium in our patients. However, symptomatic hypercalcemia was reported in two of 24 patients [21], with serum calcium of 3 to 3.5 mmol/L, and in several case reports [5,24,25].

The mechanism of hypercalcemia in active tuberculosis is still not clearly understood. The general opinion is that it represents a hypersensitivity to vitamin D that is further aggravated by high vitamin D intake [14,26]. This view is supported by Shai et al [27] who documented hypercalcemia in eight of ten tuberculous patients given vitamin D supplements. Isaacs et al [24] found raised serum levels of 1,25-dihydroxy vitamin D₃ in tuberculous patients. The link between the clinical activity of tuberculosis and the presence of hypercalcemia could be clarified by the work of Cadranet et al [28] who found that inflammatory alveolar cells, obtained by bronchoalveolar lavage, have the capacity to synthesize 1,25 dihydroxy vitamin D₃. This was associated with a persistent lymphocytic alveolitis in the lung. However, the extrarenal production of 1,25 (OH)₂ D₃ was not considered the principal mechanism of the hypercalcemia [28]. Both Cipola et al [25] and Sullivan et al [29] found normal serum levels of 1,25 (OH)₂ D₃ in cases of hypercalcemia secondary to active tuberculosis. It is postulated that the inflammatory cells of tuberculous alveolitis release osteoclast-activating factor and prostaglandins which, in turn, mobilize calcium from the bones [28].

Our finding of hypercalcemia despite a well-documented prevalence of vitamin D deficiency in Saudi Arabia [15] supports the view that the hypercalcemia does not result from an increased dietary intake of vitamin D.

References

1. Johnson NM, Shneerson G. Hypercalcemia and hypercaleiuria associated with pulmonary tuberculosis. *Br J Dis Chest* 1980;74:201-2.
2. Gerritson J, Knol K. Hypercalcemia in a child with miliary tuberculosis. *Eur J Pediatr* 1989;148:650-1.
3. Sharma OP, Lamon J, Winsor D. Hypercalcemia and tuberculosis (letter). *JAMA* 1972;222:582.
4. Braman SS, Goldman AL, Schwarz MI. Steroid-responsive hypercalcemia in disseminated bone tuberculosis. *Arch Intern Med* 1973;132:269-71.
5. Need AG, Phillips PJ, Chiu FTS, Prisk HM. Hypercalcemia associated with tuberculosis. *Br Med J* 1980;280:831.
6. Reiner M, Sigurdsson, Nunziata V, et al. Abnormal calcium metabolism in normocalcaemic sarcoidosis. *Br Med J* 1976;2:1473-6.
7. Lee JC, Catanzaro A, Parthemore JG, et al. Hypercalcemia in disseminated coccidioidomycosis. *N Engl J Med* 1977;297:431-3.
8. Walker JV, Baran D, Yakub YN, Freeman RB. Histoplasmosis with hypercalcaemia, renal failure, and papillary necrosis: confusion with sarcoidosis. *JAMA* 1977;237:1350-2.
9. Stoeckle JD, Hardy HL, Weber AL. Chronic beryllium disease: long-term follow-up of sixty cases and selective review of the literature. *Am J Med* 1969;46:545-61.
10. Diaz-Curiel M, Fernandez-Guerrero M, Rapado A, Castriello JM. Hypercalcemia in pulmonary tuberculosis (letter). *Ann Intern Med* 1982;97(1):143.
11. Gwinup G, Randazzo G, Elias A. The influence of vitamin D intake on serum calcium in tuberculosis. *Acta Endocrinol* 1981;97:114-7.
12. British Thoracic Association. A controlled trial of six months chemotherapy in pulmonary tuberculosis. First Report: result during chemotherapy. *Br J Dis Chest* 1981;75:141-53.
13. Bell NH, Stern PH, Pantzer E, Sinha TK. Evidence that increased circulating 1 α , 25-dehydroxy vitamin D is the probable cause of abnormal calcium metabolism in sarcoidosis. *J Clin Invest* 1979;64:218-25.
14. Abbasi AA, Chemplavil JK, Farah S, et al. Hypercalcemia in active pulmonary tuberculosis. *Ann Intern Med* 1979;90:324-8.
15. Sedrani SH. Are Saudis at risk of developing vitamin D deficiency? *Saudi Med J* 1986;7(5):427-33.
16. National Tuberculosis Association of the USA. Diagnostic standards and classification of tuberculosis. New York: National Tuberculosis Association, 1961.
17. Kleeman CR, Massry SG, Coburn JW. The clinical physiology of calcium homeostasis, parathyroid hormone and calcitonine. *Calcif Med* 1971;114:16-21.
18. Baron DN, ed. A short textbook of chemical pathology. London: Hodder and Stoughton, 1973:138-9.
19. Bacchus RA, Kilshaw BH, Madkour MM, et al. Establishment of male Saudi Arabian reference ranges for biochemical analytes. *Saudi Med J* 1982;3(4):249-58.
20. El-Hazmi MAF, Al-Faleh FZ, Al-Mofleh IA, et al. Establishment of normal "reference" ranges for biochemical parameters for healthy Saudi Arabs. *Trop Geogr Med* 1982;34:323-2.
21. Kitrou MP, Phytou-Pallikari A, Tzannes SE, et al. Serum calcium during chemotherapy for active pulmonary tuberculosis. *Eur J Respir Dis* 1983;64:347-54.
22. Christensson T. Familial hyperparathyroidism. *Ann Intern Med* 1976;85:614-5.
23. Epstein S, Stern PH, Bell NH, et al. Evidence for abnormal regulation of circulating 1,25 dihydroxy vitamin D in patients with pulmonary tuberculosis and normal calcium metabolism. *Calcif Tissue Int* 1984;36:541-4.
24. Isaacs RD, Nicholson GI, Holdaway IM. Miliary tuberculosis with hypercalcemia and raised vitamin D concentrations. *Thorax* 1987;42:555-6.
25. Cipola L, Roy TM, Gardner RP. Symptomatic hypercalcemia in active pulmonary tuberculosis. *J Ky Med Assoc* 1989;87:13-6.
26. Bradley GW, Sterling GM. Hypercalcemia and hypokalemia in tuberculosis. *Thorax* 1978;33:464-7.
27. Shai F, Baker RK, Addrizzo JR, Wallach S. Hypercalcemia in mycobacterial infection. *J Clin Endocrinol* 1972;34:251-6.
28. Cadranet J, Hance AJ, Milleron B, et al. Vitamin D metabolism in tuberculosis. Production of 1,25(OH)₂D₃ by cells recovered by bronchoalveolar lavage and the role of this metabolite in calcium homeostasis. *Am Rev Respir Dis* 1988;138:984-9.
29. Sullivan JN, Salmon WD. Hypercalcemia in active pulmonary tuberculosis. *South Med J* 1987;80:572-6.

PULMONARY TUBERCULOSIS IN DIABETIC PATIENTS

Lalit Pandya, MSc, MD, MRCP(UK), MRCP(Ireland);
Nasser Al-Sharif, MD, DTM&H(Liverpool), DTM(London);
Ali Maraey MSc, (TCD); Sulaiman Al-Majed, FRCP(C);
Mahmood El-Sakka, MSc, (TCD); FCCP

أجريت دراسة استطلاعية على ١٥٦٦ حالة سل رئوي، وتبين وجود داء السكري في ١٣٦ مريضاً (نسبة انتشار ٨,٧٪). كان عدد الذكور ١٠٠ والإناث ٣٦، ومتوسط عمر المرضى ٥٢ عاماً. وبلغ عدد السعوديين منهم ٩٤ مريضاً (٦٩٪). بلغت نسبة انتشار داء السكري بين المرضى السعوديين ١٣٪ بينما كانت بين المرضى غير السعوديين ٥٪ ($P < 0.005$) استغرق تحويل القشع إلى السلبية حوالي ٤٦ يوماً. بلغت نسبة انتشار الآفات في الساحة السفلى للرئة ١٩٪. بلغ عدد المرضى الذين يعتمدون على الأنسولين ٩٣ مريضاً (٦٨,٤٪) والذين يعتمدون على عقاقير خافضة للسكر بطريق الفم ٢٥ مريضاً (١٨,٩٪) والذين يعتمدون على الحمية فقط ١٨ مريضاً (١٣,٢٪). وجرى تحويل القشع إلى سلبية لدى مائة مريض من أصل مائة وأربعة من المرضى كان فحص القشع لديهم إيجابياً، وكان التحول عقب العلاج بمضادات التدرن من الصنف الأول. ولم يظهر فرق ذو قيمة إحصائية في تحول القشع بين مرضى السكري وغير المصابين به.

In a retrospective study of 1566 cases of pulmonary tuberculosis, 136 were found to have diabetes mellitus for a prevalence of 8.7%. There were 100 males and 36 females, and the average patient age was 52 years. Saudis accounted for 94 (69%) of the cases. The prevalence of diabetes was 13% for Saudi patients as compared with 5% for non-Saudis ($P < 0.005$). Sputum conversion took an average of 46 days. There was a 19% prevalence of lower lung field lesions. Ninety-three (68.4%) patients were on insulin therapy, 25 (18.9%) were on oral hypoglycemics, and 18 (13.2%) were managed on diet alone. Of 104 patients who were sputum positive, 100 showed conversion after treatment with first-line antitubercular drugs. There was no statistically significant difference in the sputum conversion between diabetic and nondiabetic patients.

Tuberculosis is one of the common infectious diseases among the populace of the Kingdom of Saudi Arabia [1-3], and diabetes mellitus also represents a common disease [4-6]. The frequent association of pulmonary tuberculosis with diabetes mellitus has long been an accepted fact [7].

Pulmonary tuberculosis is known to develop

easily and progress rapidly in untreated diabetics [7,8]. However, many Saudi diabetics go undetected for a considerable time because they do not exhibit the classic symptoms of polyuria and polydipsia [5]. These undiagnosed diabetics are susceptible to tuberculosis, especially those with severe as opposed to mild diabetes [9]. Boucot et al [10] found a markedly higher incidence of pulmonary tuberculosis in patients taking at least 40 units of insulin daily than in those taking less.

As far as we are aware, there has been no study evaluating the infective pulmonary complications in diabetics in Saudi Arabia. Although modern short-course antitubercular chemotherapy is con-

From the Sahary Chest Hospital (Drs. Pandya, Al-Sharif, Maraey, El-Sakka), and King Khalid University Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Pandya: Sahary Chest Hospital, P.O. Box 7966, Riyadh 11472, Saudi Arabia.

Accepted for publication 12 June 1990.

sidered to be equally effective in diabetic and non-diabetic tubercular patients in the West [8], the outcome of such treatment in diabetic tubercular patients in the Kingdom has also not been evaluated. We present our experience in treating these patients.

Material and Methods

We examined the medical records for 1566 patients with pulmonary tuberculosis who were admitted to Sahary Chest Hospital, Riyadh, between July 83 and August 87. Tuberculosis was diagnosed if direct microscopy examination and culture of sputum revealed acid fast bacilli (AFB) and chest x-ray studies and tuberculin test were positive. Diagnosis of diabetes was based on WHO criteria [11]. It was the policy of the hospital to admit all patients with an AFB-positive smear. Diabetes control was monitored by blood glucose estimations using glucometers and determination of double-voided urine sugar levels. All diabetic patients were on controlled diets. Except for patients with mild diabetes, all patients were put on regular insulin therapy for two weeks. If during this time the insulin requirement was less than 30 units per day, patients were shifted to oral hypoglycemics. Patients were discharged from the hospital when three consecutive sputum samples were negative for AFB by direct microscopy. The chi-square test was used for statistical analysis [12].

Results

Of the total 1566 cases of pulmonary tuberculosis examined, we found 136 (8.7%) cases with an additional diagnosis of diabetes mellitus. There were 100 males (73.5%) and 36 (26.5%) females. Diabetic males constituted 8.3% of the total tubercular males (100/1195) and diabetic females constituted 9.7% of the total tubercular females (36/371) (Tables 1 and 2), but the difference was not statistically significant. There were 94 Saudi patients, constituting 13% of the total segment of Saudi tubercular patients (94/747), whereas non-Saudi patients constituted 5% of the total segment of non-Saudi tubercular patients (42/819). The prevalence of diabetes among Saudi patients was significantly higher ($P < 0.005$) than that in the

TABLE 1. Total tubercular patients.

	Male	Female	Total
Saudi	486	261	747
Non-Saudi	709	110	819
Total	1195	371	1566

TABLE 2. Diabetics among tubercular patients.

	Male	Female	Total
Saudi	62	32	94
Non-Saudi	38	4	42
Total	100	36	136

N.B. The differences between Saudi and non-Saudi males and females are statistically significant at $P < 0.005$.

TABLE 3. Age: distribution.

Age (yr) ^a	No. of males	No. of females	Total(%)
21-30	4	1	3.7
31-40	22	4	19.1
41-50	25	12	27.2
51-60	30	8	27.9
61-70	15	6	15.4
71-80	4	5	6.6
Total	100	36	

^aAverage age, 52 years.

TABLE 4. Chest x-ray findings.

Lesion	Number(%)
Bilateral diffuse	42(30.8)
Lower lung field	26(19.1)
Bilateral upper zone	18(13.2)
Right apex	16(11.9)
Left lung, more than 2 zones	15(11.0)
Right lung, more than 2 zones	12(8.8)
Left apex	5(3.7)
Pleural effusion	2(1.4)
Total	136

TABLE 5. Extent of the lesion on chest x-ray study.

Lesion	Saudi Number(%)	Non-Saudi Number(%)
Minimal	8(8.5)	12(28.6)
Moderately advanced	32(34.0)	17(40.5)
Far advanced	54(57.5)	13(30.9)
Total	94	42

non-Saudis. The age distribution of the patients is shown in Table 3.

Sixty-six percent of the Saudi patients were males, and 13% had diabetes mellitus as compared with 5.3% of non-Saudi males ($P < 0.005$). The prevalence of diabetes among Saudi females was 12.26%, compared with 3.6% among non-Saudi females ($P < 0.001$). The sputum smear was positive in 112 (82.35%). Sputum conversion, as assessed by direct microscopy, took an average of 46 days. The average hospital stay was 48 days, and four patients (2.9%) died during their hospitalization.

Of 104 positive cases, sputum conversion took place in 100 (96.1%) within three months of treatment. Ninety-three patients (68.4%) were treated with insulin, 25 (18.4%) with oral hypoglycemic drugs, and 18 (13.2%) with diet alone.

Chest x-ray study findings are summarized in Table 4. Lower lung field lesions were found in 19.1%. We used criteria established by the National Tuberculosis Association of the U.S. [13] to determine the extent of the lesion and findings are given in Table 5. A cavitary lesion was found in 48 (51%) of the Saudis and in 18 (43%) of the non-Saudis.

Discussion

The combination of diabetes and pulmonary tuberculosis was first noticed by the eminent Arab physician Avicenna (980-1027).

The co-existence of the two diseases is considered to be mutually detrimental to both. In the 1920s and 1930s in America, tuberculosis was found to be three to sixteen times more common among diabetics than among nondiabetics [8]. In 1946, a study done in Philadelphia showed pulmonary tuberculosis in 8.4% of diabetics as compared with 4.3% in nondiabetics.

Tuberculosis per se may derange carbohydrate metabolism [14]. Treatment of tuberculosis with isoniazid, rifampicin, and pyrazinamide may interfere with the proper management of diabetes [15]. Isoniazid is known to lead to false low readings for urine sugar estimations [16]. Rifampicin is known to induce secretion of liver microsomal enzyme [17,18] and its use has been observed to decrease the serum concentration of tolbutamide by 49% and its half-life by 43%. Increased dosage

requirements of chlorpropamide have also been observed in patients taking rifampicin [18]. Conversely there is a danger of hypoglycemia if rifampicin is stopped suddenly without adjusting the dose of chlorpropamide.

The occurrence of combination pulmonary tuberculosis and diabetes correlates with the prevalence of each disease in a population. The incidence of diabetes was 12.6% in our Saudi patients. The incidence of diabetes in the Saudi population is 4.95% [19] and the accompanying incidence in Saudi tubercular patients is two and half times higher. The same high incidence exists for both Saudi males and females. This is contrary to that reported for Joslin's Clinic [8] whose patients with tuberculosis did not show an increased incidence of diabetes. The lower incidence of diabetes in non-Saudi patients, compared with Saudi patients, may be due to their relative fitness and younger age, as most have preemployment medical examinations in their own country before they come to the Kingdom.

It has been reported that diabetes is more common in Saudi males above the age of 35 years [5], and we also noticed this trend in our Saudi tubercular patients with diabetes.

Sputum positivity was found in 82.35% of the diabetics as compared with 74.0% in non-diabetics ($P < 0.05$). This agrees with findings reported for the Philadelphia survey [8]. A correlation between the severity of diabetes and the presence of active tuberculosis was also found in this study [8]. The average sputum smear conversion time for diabetic patients was 46 days, compared with 42 days for nondiabetic patients [20].

The hospital stay of the diabetic patients in our study was 10 days longer than that reported for nondiabetics [20], and is due to delay in sputum conversion and the need to adjust diabetic treatment before discharge.

The response to first-line antitubercular drugs consisting of streptomycin or ethambutol, rifampicin, isoniazid, and pyrazinamide given for two months initially and then isoniazid and rifampicin administered for seven months was quite good, as evidenced by sputum conversion in 96.1% cases within the first three months, compared with 98% in nondiabetic patients [20]. This favorable response in Saudi diabetics was also noted in a small preliminary study conducted in Taif [21].

No patient in our study had diabetic ketoacidosis, though pulmonary tuberculosis is reported as a cause of diabetic ketoacidosis even in non-insulin-dependent Saudi patients [22]. Four patients died, and the cause of death in two was related directly to extensive pulmonary tuberculosis whereas other causes not related to diabetes or tuberculosis were seen in the other two patients. Among nondiabetic tubercular patients, 3.45% died in our study [20].

Diabetic tubercular patients are known to have more extensive pulmonary lesions. In our study, 30.8% of the patients had extensive bilateral involvement exhibiting various combinations in the upper, mid, and lower zones. The number of lower-lung-field cases of tuberculosis was significantly higher than that for nondiabetic patients, as we have previously shown [23]. The number of far advanced lesions in diabetics was also more than those seen in nondiabetics ($P < 0.005$), as we have previously shown as well [20]. This higher rate of far advanced lesions in Saudis ($P < 0.005$) is coupled with the occurrence of more extensive lesions.

Acknowledgment

We are grateful to Prof. Abu Ashia, King Khalid University Hospital, Riyadh, for reviewing the manuscript and Mr. Esak Devadoss for typing it.

References

1. Aneja KS. Assignment report—tuberculosis in Saudi Arabia. WHO report: WHO-EM/TB/164, 1984.
2. Shanks NJ, Al-Kalaid KI. Tuberculosis in Saudi Arabia. Saudi Med J 1983;4(2):151-6.
3. Gunawardena KA. An update on the management of TB. Presented at the 2nd Annual Symposium on Advanced Medicine, 17-19 September 1989, Armed Forces Hospital, Riyadh.
4. Bell JL, Ghang P. Glycosuria and diabetes mellitus in Saudi Arabia. Saudi Med J 1982;3(4):284-90.
5. Bacchus RA, Bell JL, Madkour M, Kilshaw B. The prevalence of diabetes mellitus in male Saudi Arabs. Diabetologia 1982;23:330-2.
6. El-Hazmi MAF, Warsy AS. A comparative study of hyperglycemia in different regions of Saudi Arabia. Ann Saudi Med 1989;9(5):435-8.
7. Heaf FRG, ed. Symposium on tuberculosis. London: Cassell and Company, 1957;418-21.
8. Marble A, Krall LP, Bradley RF (eds). Joslin's diabetes mellitus, ed 12. Philadelphia: Lea & Febiger, 1985;741-2.
9. Pagel W, Simmonds FAH, McDonald N, Nassaue E. Pulmonary tuberculosis, ed 4. London: Oxford University Press, 1964;335.
10. Boucot KR, Cooper DA, Dillon EC, et al. Tuberculosis among diabetics: the Philadelphia survey. Rev Tuberculosis 1952(Suppl);65:127.
11. World Health Organization Expert Committee on Diabetes Mellitus. WHO Tech Rep Ser 1980;No. 646.
12. Hill AB. Short textbook of medical statistics, ed 9. London: Hodder and Stoughton, 1983;137-44.
13. Seaton A, Seaton D, Leitch AG. Classification of extent of the disease. In: Crofton & Douglas. Respiratory diseases, ed 4. Oxford: Blackwell 1989;409-10.
14. Abdel-Kader MM, Abdou Solieman, Abdel-Hafez. Some studies of intermediary carbohydrate metabolism in chronic chest disease. Egypt J Chest Dis Tuberculosis 1981;24(1-2):129-42.
15. Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics, ed 5. 1975;1212.
16. Lawrence DR, Bennett PN. Clinical pharmacology, ed 5. Edinburgh, London: Churchill Livingstone, 1985;819-20.
17. American Thoracic Society. Treatment of tuberculosis and tuberculosis infection in adults and children. Am Rev Resp Dis 1986;134(2):355-63.
18. Reynolds Martindale JEF. The extra pharmacopoeia, ed 28. London: The Pharmaceutical Press, 1982;800,860.
19. Fatani HH, Mira SS, El-Zubier AG. The prevalence of diabetes mellitus in urban Saudi Arabia. In: Niliyant W, Vichaynat A, Vannasaeng S. Diabetes Mellitus. (Proceedings of the 3rd World Congress on Diabetes in the Tropics and Developing countries, Bangkok). 1985.
20. Pandya L, Al-Sharif N, Madani A. A review of 1566 cases of pulmonary tuberculosis admitted to a Ministry of Health Chest Hospital in Riyadh (abstract). Ann Saudi Med 1988;8(6):525A-6A.
21. El-Bokhary MS. Short course chemotherapy of newly diagnosed patients with pulmonary tuberculosis in Taif Chest Hospital (preliminary report) (abstract). Ann Saudi Med 1988;8(6):523A.
22. Mira SA, Fatani HH, El-Zubier AG, El-Sabbagh S. Diabetic ketoacidosis: a report of 123 Saudi diabetics. Saudi Med J 1987;8(4):364-8.
23. Pandya L, Al-Sharif MA, Maraey A, Madani A. Lower-lung-field tuberculosis in Saudi Arabia. Ann Saudi Med 1990;10(4):374-7.

ACUTE RENAL FAILURE IN NEONATES: A PROSPECTIVE STUDY

Howaida M. A. M. Al-Idressy, MBBS;
Omer B. Abdel Basit, MRCP; Khalid N. Haque, FRCP;
Murtala B. Abdurrahman, FRCPC

أجريت دراسة على الأطفال الذين أدخلوا وحدة العناية المركزة للمواليد وأصيبوا بقصور كلوي حاد وذلك لتحديد سبب الاضطراب ومساره ونتيجته ولمعرفة إمكانية الوثوق بالمناسب الكلوية لتمييز القصور الكلوي الناجم عن الكلية ذاتها من القصور الناجم عن نقص التروية الكلوية. بلغ وقوع القصور الكلوي الحاد الوليدي ٣,٦٪ (٢٢/٦٠٣)، وكانت الأسباب الأكثر تواتراً هيبوط الضغط (٨٦٪) ومتلازمة ضائقة التنفس (٤١٪) والانتان (٣٢٪) والاختناق (٢٧٪). ولد نصف المرضى بعد حمل دام أقل من ٣٢ أسبوعاً وبوزن يقل عن ١٥٠٠ غم، وأصيب خمسة عشر (١٥) وليداً بقصور كلوي داخلي وسبعة بقصور ناتج عن نقص التروية. ولم تكن المناسب الكلوية (نسبة أسمولية البول إلى البلازما ونسبة إفراز الصوديوم ومنسب القصور الكلوي) موثوقة للتمييز بين القصور الداخلي والقصور الناتج عن نقص التروية. كانت الوفيات من القصور الكلوي مرتفعة (٧٧٪). لكن لم يلاحظ بقاء خلل كلوي لدى متابعي الناجين من القصور الكلوي الحاد الوليدي ممن لم تكن شذوذات السبيل البولي مسئولة عن حالتهم. من المهم تحديد المناسب السريرية التي يمكن استخدامها لتحديد تشخيص وإنذار القصور الكلوي الحاد وبخاصة لدى الخدج منخفضي الوزن.

Babies admitted to a neonatal intensive care unit in whom acute renal failure developed were studied prospectively to determine the etiology, course, and outcome of the disorder, as well as the reliability of renal indices in distinguishing intrinsic from prerenal renal failure. The incidence of neonatal acute renal failure was 3.6% (22/603). The most frequent causes were hypotension (86%), respiratory distress syndrome (41%), sepsis (32%), and asphyxia (27%). Half of the patients were born at less than 32 weeks' gestation and had a birth weight of less than 1500 gm. There was intrinsic renal failure in 15 neonates and prerenal failure in seven. Renal indices (urine-to-plasma ratio of osmolality, fractional excretion of sodium, and renal failure index) were not reliable in differentiating between intrinsic or prerenal failure. Mortality from renal failure was high at 77%. Survivors of neonatal acute renal failure who had no underlying congenital anomalies of the urinary tract did not appear to exhibit residual renal impairment during follow-up evaluation. It is important to identify those clinical indices that can be used in determining the diagnosis and prognosis of acute renal failure in neonates, particularly in very premature, low-birth-weight babies.

From the Department of Pediatrics, King Khalid University Hospital, Riyadh.

Address reprint requests and correspondence to Prof. Abdurrahman: Department of Pediatrics, Faculty of Medicine, and Health Sciences, P.O. Box 17666, Al Ain, United Arab Emirates.

Accepted for publication 12 June 1990.

Acute renal failure (ARF) in neonates poses a unique diagnostic and therapeutic challenge because it occurs in a setting of immature renal function characteristic of the normal newborn. The frequency of ARF in neonates varies widely, from 3% [1] to 23% [2], and the mortality, which ranges between 45% [2] and 90% [3], remains

high. ARF in neonates appears to be on the increase, partly because advances in neonatal care have resulted in an increased survival of high-risk, premature, low-birth-weight babies who would previously have died. Management of these babies often involves the use of drugs, ventilatory support, and surgery, each of which may have a profound adverse effect on renal perfusion and function.

King Khalid University Hospital has a busy 24-cot neonatal intensive care unit (NICU) with a bed occupancy of 75 to 150%. We conducted a prospective study to document the causes, course, and outcome of ARF in neonates. We also determined the reliability of renal indices in differentiating intrinsic from prerenal failure.

Patients and Methods

Any infant admitted to NICU who suffered ARF was eligible for enrollment in the study. ARF was defined as the persistence of oliguria (urine output, < 1 ml/kg/hr) for more than 12 hours and/or serum creatinine level of 90 μ mol/L and rising. The following data were recorded for each baby: gestational age, birth weight, prenatal and postnatal history, findings on physical examination, onset of renal failure, other diagnoses, hospital course, and outcome. First-voided urine specimen after the onset of ARF was obtained for dipstick analysis as well as microscopic examination and determination of osmolality and levels of sodium, creatinine, and urea. Blood was taken at the same time for determination of osmolality as well as concentrations of electrolytes, creatinine, and urea. Hematological investigations included full blood count, prothrombin time, and partial thromboplastin time. Arterial blood gases were determined, and portable renal ultrasonography was done.

Oliguric patients who had no evidence of circulatory overload underwent a fluid challenge test. The test consisted of an intravenous infusion of 20 ml/kg of plasma or 0.45% saline in 10% glucose administered over an hour, followed by 4 mg/kg furosemide given intravenously. The urine output was observed for the next four hours. The challenge test was considered positive if urine output was at least 2 ml/kg/hr, indicating prerenal failure. A urine output of less than 2 ml/kg/hr was inter-

preted as negative, and indicated intrinsic renal failure. Urine and blood samples for osmolality and chemistry evaluations were obtained before doing a fluid challenge test. Standard laboratory methods were used for all tests. Urine-to-plasma ratio (U/P) of osmolality, fractional excretion of sodium (FENa), and renal failure index (RFI) were calculated from these initial investigations:

$$\text{FENa} = \frac{\text{UNa/SNa}}{\text{Ucr/Scr}} \times 100$$

$$\text{RFI} = \frac{\text{UNa}}{\text{Ucr/Scr}}$$

where *UNa* and *SNa* represent urine and serum sodium concentration (mmol/L), respectively, and *Ucr* and *Scr* represent urine and serum creatinine concentration (mmol/L), respectively. An FENa of > 3% or RFI of > 3 was considered to indicate intrinsic renal failure, while values less than these were considered to indicate prerenal failure [1,2]. A U/P osmolality of < 1 signified intrinsic renal failure, and ≥ 1 was indicative of prerenal failure [2]. A baby of the same sex, gestational age, and weight who did not have renal failure was selected as a control.

Results

The study period lasted for 25 months, extending from February 1986 to March 1988. ARF was diagnosed in 22 neonates out of 603 admissions, yielding an incidence of 3.6%. There were 14 males and 8 females for a ratio of 1.8:1. This ratio is slightly higher than the 1.3:1 found overall for NICU admissions. The gestational age of the patients was 33 ± 6 weeks (mean $\pm$ SD), and birth weight, 1788 ± 959 gm. Corresponding values for the control group of 14 neonates (eight males and six females) were 32 ± 1.6 weeks and 1723 ± 276 gm. The frequency distribution of ARF in relation to gestational age and to birth weight (Figure 1) shows a bimodal pattern: one peak occurred in the very premature low-birth-weight neonates and the other in term babies. ARF in term infants was more often associated with sepsis, with or without disseminated intravascular coagulation. Age at onset of ARF varied from one to 24 days (median,

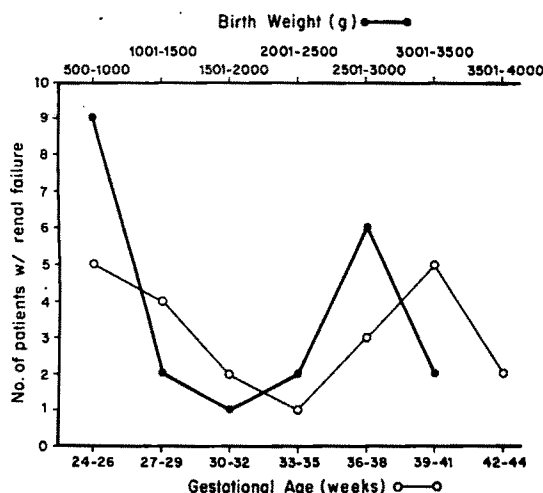


FIGURE 1. Frequency of acute renal failure according to birth weight and gestational age.

TABLE 1. Conditions associated with acute renal failure in the newborn.

Associated clinical conditions	No. of patients	(%)
Hypotension	19	(86)
Respiratory distress syndrome	9	(41)
Sepsis	7	(32)
Perinatal asphyxia	6	(27)
Patent ductus arteriosus	5	(23)
Intraventricular hemorrhage	5	(23)
Disseminated intravascular coagulation	4	(18)
Others	3	(18)

3 days). The onset occurred over 1 to 5 days in 15 (68%) patients. Conditions associated with renal failure are listed in Table 1. More than one factor was present in every patient. The most frequent conditions were hypotension (86%), respiratory distress syndrome (41%), sepsis (32%), and asphyxia (27%). One premature baby with patent ductus arteriosus was treated with indomethacin, and this was suspected as the possible cause of his renal failure.

Because none of the babies had evidence of circulatory overload, all underwent fluid challenge. ARF was classified as intrinsic renal failure in 15 cases because of a negative fluid challenge test. Renal indices could not be calculated in seven patients because they were anuric. The scattergram in Figure 2 shows that neither U/P osmolal-

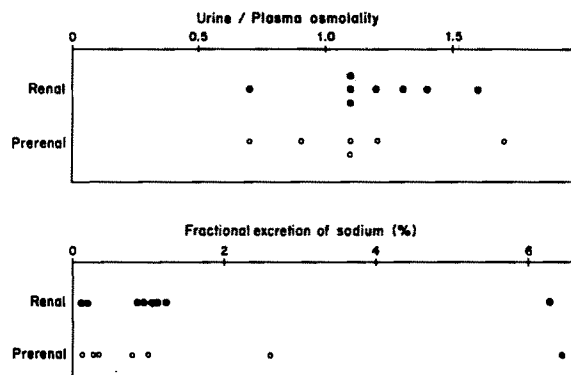


FIGURE 2. Urine-plasma ratio of osmolality and fractional excretion of sodium in newborns with renal failure.

ity nor FENa was reliable in differentiating intrinsic from prerenal renal failure. This was due to considerable overlap in the values of the indices between patients with intrinsic renal failure and those with prerenal renal failure. The pattern obtained for RFI was similar to that for FENa. In patients who had intrinsic renal failure, the mean $\pm$ SD values for U/P osmolality was 1.1 ± 0.3 ; for FENa, 1.5 ± 2.0 ; and for RFI, 1.9 ± 2.5 . These values were not significantly different from those obtained in patients with prerenal renal failure, in whom U/P osmolality was 1.2 ± 0.4 ; FENa, 1.6 ± 2.3 ; and RFI, 2.1 ± 3.1 .

Renal ultrasonography was normal in 10 of 16 patients. Of the remaining six patients, four showed hyperechogenicity, one nephromegaly, and one unilateral renal agenesis. No abnormality of the lower urinary tract was detected.

Management

Patients who did not respond to fluid challenge were treated with restricted fluid intake. The fluid volume given was equal to urine output plus insensible fluid loss (30 ml/kg body weight) and any ongoing losses from diarrhea or vomiting. Metabolic acidosis was partially corrected with intravenous sodium bicarbonate. The amount of sodium bicarbonate required for total correction of metabolic acidosis was calculated from the formula:

$$\frac{\text{body weight (kg)} \times \text{base deficit}}{3}$$

half of this amount was given for partial correc-

TABLE 2. *Current status of survivors of neonatal acute renal failure.*

Gestational age (wk)	Diagnosis	Type of renal failure	Age (yr)	Current status
28	LBW, prematurity, anemia, hypotension	Prerenal	3.5	No renal impairment, bronchopulmonary dysplasia
28	LBW, prematurity, intravascular hemorrhage	Intrinsic	3.5	No renal impairment, bronchopulmonary dysplasia, retinopathy of prematurity
30	LBS, prematurity, sepsis, PDA	Intrinsic	4	Well, no renal impairment
40	Severe birth asphyxia, convulsion	Prerenal	3	Well, no renal impairment
42	Spontaneous pneumothorax, premature rupture of membranes, right renal agenesis	Prerenal	2.5	Chronic renal failure, right renal agenesis

LBW = low birth weight.

tion. The initial treatment of hyperkalemia consisted of administration of insulin plus glucose or intravenous calcium, followed by ion exchange using resin calcium polystyrene sulfonate. Six patients underwent peritoneal dialysis, which was started between one and five days after the onset of ARF. Three of them had a gestational age of ≤ 30 weeks and a birth weight of ≤ 1000 gm. Two patients had sepsis and disseminated intravascular coagulation, and the sixth had severe perinatal asphyxia and hypotension. The indications for peritoneal dialysis were: progressive uremia, intractable hyperkalemia, and severe fluid overload. The only complication encountered was an episode of peritonitis in one patient. All six patients died.

Outcome

Seventeen patients died, yielding an overall mortality rate of 77%. Four of the seven patients with prerenal failure died, compared with 13 of the 15 patients with intrinsic renal failure. The exact cause of death could not be determined with certainty in most cases because several contributory factors (Table 1) were also operant. ARF was not considered to have been directly involved in

the death of four patients, one of whom died some days after ARF had resolved. The five survivors were followed up for from three months to 3.5 years. Their status at the last assessment is summarized in Table 2.

Discussion

The data in the present study show that ARF is not uncommon in our NICU, particularly in premature low-birth-weight babies. It occurs in critically ill infants with multiple organ dysfunction. In the context of respiratory distress syndrome, several possible causes may be responsible. These include hypoxemia, impaired ability to excrete free water, hypotension and hemodynamic changes, and interference with normal kidney differentiation and maturation. The implication of treatment modalities in the cause of renal failure also cannot be excluded, as babies with respiratory distress syndrome are sometimes treated with mechanical ventilation which may cause hemodynamic changes in the kidney.

Although nonoliguric ARF is now increasingly recognized, even in neonates [4], it was not seen in any of our patients. It is unlikely that the diagnosis

was missed because meticulous intake-output records are maintained for all patients in our NICU, and serum creatinine and electrolyte concentrations are determined routinely. Our patients were a highly selected group, in that 11 (50%) had a gestational age of ≤ 32 weeks and a correspondingly very low-birth-weight (see Figure 1). This fact could explain two of our findings, namely, the high morbidity and mortality plus the lack of reliability of renal indices in distinguishing between intrinsic ARF and prerenal renal failure. Very premature infants have a high urinary sodium excretion with correspondingly high FENa, which decreases exponentially with both gestational age and postnatal age [5,6]. The reasons postulated for salt wasting in premature infants include glomerulotubular imbalance, tubular unresponsiveness to aldosterone, and sodium and water diuresis resulting from contraction of the premature infant's large extracellular volume following birth.

Most neonates with ARF have oliguria. Therefore, obtaining urine samples for determining renal indices is delayed or impossible, as was the case in seven of our patients. This problem is compounded by the poor diagnostic yield of renal indices in premature low-birth-weight and very-low-birth-weight babies. For these reasons we advocate using the fluid challenge test in neonates with ARF who have no circulatory overload.

Peritoneal dialysis was technically successful in all six patients, including three babies who weighed less than 1000 gm. Dialysis was considered successful if there was a significant reduction in the serum levels of creatinine, urea, and potassium, a decrease in the acidosis, and a net fluid loss associated with normalization of blood pressure. The 100% mortality in patients treated with peritoneal dialysis might be partly due to starting the procedure relatively late, and partly a reflection of the patients' condition before dialysis. We have now begun to institute peritoneal dialysis early in neonates with ARF.

The prognosis for neonates with ARF is quite variable, and depends to a large extent on the primary event precipitating ARF, the extent and severity of other organ system dysfunction, and the

expertise of management. The mortality rate in infants with ARF cited in several reports is between 45 and 86% [1,2,7-9]. Although our mortality of 77% is high, it is comparable to the 90% reported recently by Meeks and Sims [3], whose population of patients was similar to ours.

Four of the five survivors have continued to show no evidence of renal impairment, as confirmed by normal isotopic renogram and normal serum creatinine and biochemistry findings. The fifth patient, who has chronic renal failure, has unilateral renal agenesis. Our findings, however, are limited by the small number of patients. Moreover, glomerular and tubular dysfunction as well as chronic renal failure have been described in survivors of neonatal ARF [1,8,10].

Our findings as well as those of other workers indicate a need for relatively simple but reliable clinical and laboratory criteria for determining the diagnosis and prognosis of ARF in neonates, particularly in very premature low-birth-weight infants.

References

1. Stapleton FB, Jones DP, Green RS. Acute renal failure in neonates: incidence, etiology and outcome. *Pediatr Nephrol* 1987;1:314-20.
2. Norman ME, Asadi FK. A prospective study of acute renal failure in the newborn infant. *Pediatrics* 1979;63:475-9.
3. Meeks ACG, Sims DG. Treatment of renal failure in neonates. *Arch Dis Child* 1988;63:1372-6.
4. Grylack L, Medani C, Hultzen C, et al. Nonoliguric acute renal failure in the newborn: a prospective evaluation of diagnostic indexes. *Am J Dis Child* 1982;136:518-20.
5. Ross B, Cowett RM, OH W. Renal function of low birth weight infants during the first two months of life. *Pediatr Res* 1977;411:1162-4.
6. Arant BS Jr. Developmental patterns of renal functional maturation compared in the human neonate. *J Pediatr* 1978;92:705-12.
7. Mathew OP, Jones AS, James E, et al. Neonatal renal failure: usefulness of diagnostic indices. *Pediatrics* 1980;65(1):57-60.
8. Ellis EN, Arnold WC. Use of urinary indexes in renal failure in the newborn. *Am J Dis Child* 1982;136:615-7.
9. Chevalier RL, Campbell F, Brenbridge ANAG. Prognostic factors in neonatal acute renal failure. *Pediatrics* 1984;74:265-72.
10. Reimold EW, Don TD, Worthen HG. Renal failure during the first year of life. *Pediatrics* 1977;59(suppl):987-94.

INSULIN-DEPENDENT DIABETES MELLITUS IN CHILDREN: FAMILIAL AND CLINICAL PATTERNS IN RIYADH

Hussein Salman, MD; Ahmed Abanamy, MD;
Basset Ghassan, DHC;
Mohammed Khalil, MSc(Com Med), MSc(Ped)

قد يكون الداء السكري من النوع ١- من الأمراض الشائعة في المملكة العربية السعودية، ولكن المعلومات المتوافرة عن هذه المرض محدودة جداً، إذ أن معظم الحالات المسجلة حتى الآن هي عن داء السكري من النوع ٢- . تم تشخيص داء السكري من النوع ١- في ١١٠ أطفال ممن كانوا يراجعون مستشفى الأطفال بالسليمانية لمتابعة حالتهم طوال خمس سنوات (١٩٨٥ - ١٩٨٩م). كانت نسبة السعوديين بينهم ٧٤,٥% (٨٢/١١٠)، ونسبة الإناث ٥٣,٦% (٥٩/١١٠). كانت هناك صلة قرى بين الأبوين في ٤٢,٧% (٤٧/١١٠) من الحالات. كانت قصة القرى من الدرجة الأولى في العائلة في حالات مرضى السكري المعتمدين على الأنسولين إيجابية بنسبة ٢٨,١% (٣١/١١٠). كان متوسط العمر عند بداية المرض ٥,٨٧ سنة، وهو منخفض مقارنة بالأعمار الأخرى المدونة في الأدبيات الطبية. ثلاثة وثلاثون مريضاً (٣٠%) كانوا دون الثالثة من العمر عند بداية المرض. وكانت أكثر العلامات السريرية شيوعاً هي الحمض الكيتوني الذي لوحظ وجوده في ٦٧,٢% (٧٤/١١٠) من الحالات. تراوحت مدة الأعراض قبل التشخيص من يومين إلى أكثر من شهرين، بمتوسط ١٨,٢ يوماً، ولوحظت هذأة جزئية في ٣٠,٩% (٣٤/١١٠) من الحالات. إن سبب هذه النسبة المنخفضة يعود في الغالب إلى صغر السن عند حدوث المرض وربما إلى نمط مختلف من حدة المرض في مجتمعنا. وتدعو الحاجة إلى إجراء المزيد من الدراسات، بها في ذلك فتح سجل محلي، لتأكيد نسبة وقوع المرض وخصائصه في المملكة العربية السعودية.

Type I diabetes mellitus is probably common in Saudi Arabia, but only a small amount of information on the disease is available and most cases reported so far have been type II diabetes mellitus. Type I diabetes was diagnosed in 110 children who were followed at Suleimania Children's Hospital over a five-year period (1985-1989). Saudis represented 74.5% (82/110) of the patients, and 53.6% (59/110) were female. Consanguinity existed in 42.7% (47/110) of the parents. A first-degree family history was positive for insulin-dependent diabetes mellitus in 28.1% (31/110). Mean age at onset was 5.87 years, which is low compared with other ages cited in the literature. Thirty-three patients (30%) were below three years of age at onset. The most common clinical sign was diabetic ketoacidosis, which was seen in 67.2% (74/110). Duration of symptoms before diagnosis ranged from two days to more than two months, with a mean of 18.2 days. Partial remission was seen in 30.9% (34/110). This low percentage is probably due to the young age distribution at onset and perhaps to a different pattern of severity of the disease in our community. Further studies, including opening a local registry, are needed for confirming the incidence and characteristics of the disease in Saudi Arabia.

From Suleimania Children's Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Salman: Suleimania Children's Hospital, P.O. Box 59046, Riyadh 11525, Saudi Arabia.

Accepted for publication 25 June 1990.

Several epidemiological surveys have shown that the prevalence of diabetes mellitus type I is steadily increasing and that the number of diabetics is approximately doubling every decade [1-4]. The epidemiology and characteristics of diabetes mel-

litus, particularly insulin-dependent diabetes mellitus, are not well known in the Saudi community and only a few data are available.

We conducted a retrospective descriptive, hospital-based study to elucidate some of the patterns of the disease in the Riyadh population.

Patients and Methods

We studied 110 diabetic children seen at Suleimania Children's Hospital during a five-year period (1985–1989). Age at onset, sex, nationality, consanguinity, family history of diabetes mellitus (first- and second-degree parents), clinical presentation, duration of symptoms before diagnosis, and partial remission rate were recorded.

Diagnosis was based on clinical (e.g., polyuria, polydipsia, loss of weight, fatigability) and biological features (e.g., significant hyperglycemia, considering the National Diabetes Data Group criteria [1,2] of fasting blood glucose of more than 140 mg/dl [7.7 mmol/L] and postprandial blood glucose level at two hours of more than 200 mg/dl [11.1 mmol/L], and glycosuria with or without ketonuria).

Diagnosis of diabetic ketoacidosis was based on clinical (vomiting, abdominal pain, acidotic breathing, moderate to severe dehydration, torpor, or coma) and biological features (hyperglycemia exceeding 15 mmol/L, ketonuria, and metabolic acidosis with a bicarbonate level of below 15 mmol/L).

Partial remission was defined according to the International Study Group of diabetes in children and adolescents criteria [2] as a period of "freedom from clinical symptoms of diabetes with insulin requirements of less than 0.5 unit/kg/day with absent or minimal glycosuria for more than 4 weeks duration."

Familial and clinical data for children below 5 years of age and 5 years of age and older were compared. Likewise the findings in diabetic children of related parents were compared with those from children of unrelated parents.

Results

The data in 110 diabetic children were reviewed. There were 82 (74.5%) Saudis and of the remaining 28 (25.4%), 13 (11.8%) were Pales-

tinian, 9 (8.2%) were Egyptian, 3 (2.7%) were Syrian, and 1 (0.9%) was Yemeni. Only two patients (1.8%) were of non-Arab origin (one was Pakistani and one was Eritrean). There were 59 (53.6%) females and 51 (46.3%) males, for a male-female ratio of 0.86. Of the 62 patients aged 5 years and older, 36 (58.06%) were female and 26 (41.9%) were male, for a male-female ratio of 0.72. Of the 48 patients in the age group below 5 years, 25 (52.08%) were male and 23 (47.9%) were female, for a male-female ratio of 1.08. There was consanguinity in 47 (42.7%) of the patients; 34 (11.8%) sets of parents were first-degree cousins and 13 (11.8%) were second-degree cousins.

There was a positive first-degree family history of insulin-dependent diabetes mellitus in 31 (28.2%) patients. Siblings of 29 (26.3%) patients were affected and two fathers were affected. None of the mothers were affected. There was a positive family history of non-insulin-dependent diabetes mellitus in the grandparents of 38 (34.5%) patients and three fathers and one mother among four patients were affected. Family history was positive for both insulin-dependent and non-insulin-dependent diabetes mellitus in 15 (13.6%) patients. Twelve families (nine Saudi, three Palestinian) had more than one diabetic child, and first-degree consanguinity existed for seven (58.3%) of the children.

Age at onset ranged from 7 months 15 days to 12 years (mean, 5.87 years). Eleven (10%) patients were below 1 year of age, 33 (30%) were below 3 years, and 48 (43.6%) were below 5 years.

The most common clinical presentation was moderate to severe diabetic ketoacidosis, present in 74 (67.3%). This percentage varies in our series, depending on the age group and existence of consanguinity: diabetic ketoacidosis was seen in 34 of the 48 (70.8%) patients below 5 years of age, compared with 40 of the 62 (64.5%) patients 5 years and older. This percentage was 70.2% (33/47) in children of related parents compared with 65.8% (41/63) in those of unrelated parents. Diabetic ketoacidosis was severe ($\text{pH} < 7.1$) in 31 of the 74 (41.9%) affected patients. The most frequent symptom was polyuria with or without polydipsia and with or without nocturia, and was noted in 83 (75.4%) patients. A single symptom was seen in four patients: nocturnal enuresis in

three (2.7%) patients and asthenia with delayed wound healing in one (0.9%). Loss of weight was found in 41 (37.3%) patients and polyphagia and anorexia each in seven (6.3%) patients. In the 33 patients in the age group below 3 years, 13 (39.4%) were referred for "flu-like" symptoms and other common symptoms of illness in infancy such as fever, diarrhea, vomiting, and dehydration. Two (1.8%) patients were diagnosed by glucose tolerance test during an episode of acute gastroenteritis after the random blood glucose level was found to be high at above 11.1 mmol/L. Four (3.6%) cases were diagnosed by screening (hemoglukotest and glucose tolerance test) in sibilings (free of symptoms) of diabetic patients.

Duration of symptoms before diagnosis ranged from two days to more than two months. In most patients (72.7%; 80/110), the interval ranged between one and four weeks. The interval was more than two months in five (4.5%) cases. In 17 patients (15.4%), most of them below 5 years of age, the interval was one week or less. Thus, the overall mean duration was 18.2 days compared with 9.7 days in the group of patients below 3 years. This mean was 12.5 days in children of related parents, compared with 20.2 in those of unrelated parents.

Familial and clinical data for diabetic children below 5 years of age and 5 years of age and older are compared in Table 1. Familial and clinical data for diabetic children of related and unrelated parents are compared in Table 2.

Partial remission occurred in 34 (30.9%) of the patients, but this rate varies among our patients depending on the age group and a family history of consanguinity. It was 33.9% in the age group above 5 years compared with 27.08% in the age group below 5 years. It was 29.8% in the children of related parents compared with 31.7% in those children of unrelated parents. Among the patients with partial remission, males represented 44.1% (15/34) and females, 55.9% (19/34). Two (5.9%) of these patients were obese. Sixteen (47.06%) presented with diabetic ketoacidosis. Their mean glycosated hemoglobin level was 12.7% compared with 14.3% for our total diabetic population. Partial remission took place between 1.5 and 7 weeks after initiation of therapy (mean, 5 weeks) and lasted for 5 to 15 weeks (mean, 9 weeks). The daily insulin dosage needed during

this period ranged from 0.25 to 0.45 unit/kg/day (mean, 0.34 unit/kg/day).

Discussion

The true incidence of insulin-dependent diabetes mellitus for the Riyadh population is not known. Most recent data consists of 15 cases registered for Riyadh Maternity and Children's Hospital between 1979 and 1983 and 60 cases registered for King Khalid University Hospital between 1983 and 1987 [5]. The present study includes 110 patients seen at Suleimania Children's Hospital over a five-year period (1985-1989), for an overall frequency of one patient presenting per month. This is an important finding that is probably related to an unexpectedly higher or increasing incidence of the disease in our community. Most of the patients were Saudi and all but two were of Arab origin.

TABLE 1. Comparative data for children above and below 5 years of age.

Variables	Children below 5 years	Children 5 years and above
Number	48/110(43.6%)	62/110(56.3%)
Related parents	25/48(52%)	22/62(35.5%)
First-degree family history of insulin-dependent diabetes mellitus	19/48(39.6%)	12/62(19.3%)
Male-female ratio	1.08	0.72
Mean duration of symptoms	10.5 days	18.5 days
Clinical presentation, diabetic ketoacidosis	34/48(70.8%)	40/62(64.5%)
Partial remission rate	13/48(27.08%)	21/62(33.9%)

TABLE 2. Comparative data between diabetic children of related and unrelated parents.

Variables	Children of related parents	Children of unrelated parents
Number	47(42.7%)	63(57.3%)
First-degree family history of insulin-dependent diabetes mellitus	22/47(46.8%)	9/63(14.3%)
Clinical presentation, diabetic ketoacidosis	33/47(70.2%)	41/63(65.08%)
Mean duration of symptoms	12.5 days	20.2 days
Partial remission rate	14/47(29.8%)	20/63(31.7%)

The male preponderance reported in the literature [1-3] and in a similar local study [5], citing a male-female ratio ranging between 1.08 and 1.15, was not observed in our series. However, the male-female ratio was 1.08 in the age group below 5 years. Other study findings have also varied with regard to the male-female ratio [5,6].

Diabetes mellitus occurs significantly more frequently in the parents and siblings of diabetics than in the control population [1,2]. In our series, both the consanguinity rate and family history of both insulin-dependent and non-insulin-dependent diabetes mellitus were higher than those reported in the literature and in a similar local study [1,2,5-7]. The father was the affected relative in two cases, but never the mother. This lower incidence of a maternal history of insulin-dependent diabetes mellitus has been reported previously [8].

The incidence of diabetes mellitus in childhood increases with age, with only a few cases occurring in infancy, and reaches a peak at around 5 to 7 years and 11 to 14 years [1,2,4,9]. The mean age at onset in our series was 5.87 which is lower than that reported elsewhere [1-3,6].

The most common clinical presentation in our series was diabetic ketoacidosis (67.2%), and this was even higher for patients below 5 years of age (70.8%) and for patients with related parents (70.2%). These figures are a cause of concern. They are approximately similar to other local and Asian figures [5,10,11] but are higher than those reported in the literature [1-3,6]. This finding is probably a reflection of an appreciable delay in diagnosis, as shown in our patients, as well as a higher incidence in our community of precipitating intercurrent infection. It may also reflect a different etiology or a different pattern of severity of the disease in Saudi children. Other symptoms observed in our series were essentially similar to the classic symptoms of type I diabetes mellitus [1,2]. However, these symptoms were overlooked by both parents and physicians in 39.3% of the children younger than 3 years.

The duration of clinical symptoms before detection varied greatly, from 10 days to several months, and older children and adolescents tended to have longer histories before detection [1,2]. In our series, diabetic children below five years of age showed a shorter duration of

symptoms and presented more acutely. This was similar in our patients of related parents.

Two to eight weeks after the onset of insulin therapy, many diabetic children, up to 75%, experienced only one temporary period of partial remission, lasting four weeks to several months [1,2,12,13]. This so-called "honeymoon period" seems to be more common in male diabetics and in obese children [1,2,12,13], but this was not observed in our study. A period of partial remission also seems more common among older children and in those presenting without ketoacidosis [1,2,12,13], as borne out by our results. It can also vary depending on the initial glycosylated hemoglobin value, as shown in our study, as well as depending on the intensity of initial insulin therapy and the pancreatic B cell residual function [1,2,12,13]. Furthermore, in our study the partial remission rate was higher in children of unrelated parents than in those of related parents. Our low remission figure, which is similar to that from other local reports [5], is probably related to the young age distribution at onset in our series and perhaps to a different pattern of severity of the disease in our community.

Our study shows that insulin-dependent diabetes mellitus is common in Riyadh, and presents some particular epidemiological and clinical features. However, further studies along with initiation of a local registry are needed to confirm these findings and foster a better understanding of the disease and a better awareness on the part of the public and pediatrician community.

References

1. Weber B. Pathophysiology of diabetes mellitus. In: Brook CGD, ed. *Clinical pediatric endocrinology*, ed 2. Oxford: Blackwell, 1989;555-82.
2. Bonnici F. Clinical management of diabetes mellitus. In: Brooks CGD, ed. *Clinical pediatric endocrinology*, ed 2. Oxford: Blackwell, 1989;599-612.
3. Lestrade H, Besse J. Prevalence and incidence of juvenile diabetes in children and adolescents [proceedings]. *Acta Paediatr* 1977;30(2):123-4.
4. Bloom A, Hayes TM, Gamble DR. Register of newly diagnosed diabetic children. *Br Med J* 1975;3(5983):580-3.
5. Abdulla MA. The clinical presentation of childhood diabetes mellitus in Riyadh, Saudi Arabia. *Saudi Med J* 1989;10(6):495-7.
6. Jefferson IG, Smith MA, Baum JD. Insulin dependent diabetes in under 5 years old. *Arch Dis Child* 1985;60(12):1144-8.

7. Wagener DK, Sacks JM, LaPorte RE, MacGregor JM. The Pittsburgh study of insulin-dependent diabetes mellitus: risk for diabetes among relatives of insulin dependent diabetes mellitus. *Diabetes* 1982;31:136-44.
8. Warram JH, Krolewski AS, Gottlieb MS, Khan CR. Differences in risks of insulin dependent diabetes mellitus in offspring of diabetic mothers and diabetic fathers. *N Engl J Med* 1984;311(3):149-52.
9. Calnan M, Peckham C. Incidence of insulin-dependent diabetes mellitus in the first sixteen years of life. *Lancet* 1977;1:589-90.
10. Bonnici F. Treatment of diabetic children in underprivileged population. In: *Proceedings of the XVIII International Congress of Pediatrics, Hawaii*. 1986;859A.
11. Khoo BH, La KL, Nagan A. Juvenile diabetes in peninsular Malaysia. In: Mimura G, Kitagawa T, Hibi I, eds. *Childhood diabetes in Asia*. Tokyo Med J 1978;92-9.
12. Akerblom HK. Definition of partial remission in insulin dependent diabetes mellitus (abstract). *Acta Paediatr Belg* 1980;33:66.
13. Baker L, Kaye R, Root AW. The early partial remission of juvenile diabetes mellitus. *J Pediatr* 1967;71:825-31.

MENINGITIS IN CHILDREN OF ELMADINA ELMUNAWARA

Eisa Osman El-Amin, MBBS, DTCH, MRCP;
El-Fatih El-Shiek Musa, MBBS, DCH;
Sabah Ali Yousif, MBBS, DCH

تمت مراجعة الملفات الطبية لمائة واثنين وعشرين مريضاً أصيبوا بالتهاب السحايا وأدخلوا إلى المستشفى خلال سنة واحدة. أكد زرع السائل النخاعي التهاب السحايا الجرثومي في ٥٩ منهم. ومن بين المرضى الثلاثة والستين الباقين كانت هناك ٣٥ حالة التهاب سحائي جرثومي، و ٢٥ حالة التهاب سحائي حموي، وثلاث حالات التهاب سحائي درني. كان ٨٢ من هؤلاء المرضى (٦٥٪) سعوديين، وكان معظمهم دون سن الخامسة. كانت المستدمية النزلية المرض الأكثر انتشاراً الذي تم عزله من المرضى الذين تقل أعمارهم عن سنة واحدة، كما كانت النيسرية السحائية هي أكثر العضويات التي تحققنا منها عموماً، ولا سيما في الحالات التي تحدث في موسم الحج. وكان زرع السائل النخاعي واختبار تراص اللاتكس هما الأكثر وثوقاً في تأكيد صحة التشخيص.

The medical records of 122 patients with meningitis admitted during one year were reviewed. Cerebrospinal fluid (CSF) culture confirmed bacterial meningitis in 59; of the remaining 63, 35 were partially treated bacterial, 25 were viral, and three were tuberculous meningitis. Eighty-two patients (65%) were Saudi and most were younger than 5 years. *Hemophilus influenzae* was the most common pathogen isolated in patients younger than one year, and *Neisseria meningitidis* was the most common organism identified overall, especially in cases occurring during the Haj. CSF culture and the latex agglutination test were the most reliable in confirming diagnosis.

Meningitis has been a recognized disease entity since Vieusseux's original description published in 1806 [1]. The causative organisms vary for different areas of the world, and the seasonally related increase is observed for several organisms [2]. In the "meningitis belt" of sub-Saharan Africa, epidemics of group A meningococcal disease occur every 8 to 12 years [3]. Saudi Arabia has frequently been affected by these epidemics, because African muslims making pilgrimage (*Haj*) to Mecca harbor the organisms. Ironically, the 1987 epidemic in this "meningitis belt" originated from Saudi Arabia with a strain introduced by South

Asians who were performing Haj [4]. The strain was designated "clone III-I" [4]. The pattern of childhood meningitis has been well documented for Riyadh [5-7] and the Eastern Province [8-12], but we are not aware of a similar analysis done for our region where the pattern may be influenced by the presence of *hajis*. This paper retrospectively studied the clinical factors and laboratory findings in cases of childhood meningitis.

Material and Methods

The records of meningitis cases encountered during one year (August 1988 to July 1989) were analyzed. Criteria for inclusion in the study were: age above one month, a positive cerebrospinal fluid (CSF) culture, and a cell count in CSF exceeding 5 per mm³, in the event of a negative CSF culture. Additional exclusion criteria were: bloody spinal tap and incomplete details for CSF

From the Department of Pediatrics, Maternity and Children Hospital, Madina Al-Munawara.

Address reprint requests and correspondence to Dr. El-Amin: Department of Pediatrics, Maternity and Children Hospital, Madina Al-Munawara, Kingdom of Saudi Arabia.

Accepted for publication 23 June 1990.

analysis regarding microscopic findings, Gram's staining, or culture.

Gram's staining was performed using the method of Cheesbrough [13] and CSF was cultured in chocolate, MacConkey, and blood agar. Wellcome bacterial antigen kits [14] were used for the latex agglutination tests, but the supply of kits was irregular and therefore the test was not done in all patients.

Bacterial meningitis in this study is defined as the presence of an organism in the CSF demonstrated by culture, Gram's staining, or latex agglutination tests. Partially treated bacterial meningitis was diagnosed if the patient had received antibiotics prior to admission and/or no organism could be demonstrated in the CSF but the CSF cell content exceeded 60% polymorphs and the CSF/blood glucose ratio was under 60%. Viral meningitis was diagnosed if no organisms were found in the CSF and the cell content was under 60% polymorphs with a CSF/blood glucose ratio greater than 60%. Tubercular meningitis was diagnosed if the patient showed features of partially treated or viral meningitis, his or her Mantoux test was positive (> 10 mm induration), and there was other evidence of tuberculosis in the patient or in his or her close relatives.

Results

A total of 165 patients were admitted with the clinical diagnosis of meningitis. Of these, case notes were missing in six and 21 proved not to have meningitis. CSF study results were incomplete in three cases and four had bloody spinal taps. This left 122 cases that met the study criteria. Saudis represented 65.1% of the group, with Pakistanis representing 12.7%; Yeminis, 5.6%; West Africans, 4%; and other nationalities, 12.6%. There was an equal number of male and

female patients; 41.3% were infants and 71.4% were below 5 years of age. The oldest child in the study was 9 years old. The average duration of symptoms prior to presentation was 69 hours (range, 6 hours to 9 days).

The admission rate was almost constant for all months of the year except for a surge in August and a dip in March (Table 1).

Clinical Presentation and Laboratory Findings

Most patients presented with the usual features of fever, vomiting, headache, and meningeal irritation. Fifty-eight were not fully conscious at presentation and four were unconscious. Convulsions had occurred in 31 patients (25.4%) and 25 of them had bacterial meningitis, mainly due to *H. influenzae* (10 patients). Thirteen patients had skin rashes and nine of them had *N. meningitidis* infection.

The average white blood cell count for bacterial infection was $18.03 \times 10^9/L$ (range, $2.8-46.8 \times 10^9/L$) and 65% of the patients had polymorphonuclear leukocytosis exceeding 60%.

Based on the study criteria, 122 cases were classified as follows: 59 bacterial, 35 partially treated bacterial, 25 viral, and three tubercular meningitis.

The breakdown of the 59 cases of proved bacterial meningitis based on CSF findings is shown in Table 2.

Thirty-eight of the 40 patients (95%) with positive Gram's staining also showed bacterial growth in CSF cultures. However, in three instances Gram's staining was negative but CSF culture revealed gram-positive organisms. False negative results of Gram's stain were seen in 19 cases (32.2%).

The latex agglutination test was done for 40 specimens and results agreed with culture findings in 26 instances. The latex agglutination test also

TABLE 1. Distribution of meningitis cases during August 1988 to July 1989.

	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July
All cases of meningitis (N = 122)	24	11	9	12	9	7	12	3	11	10	7	7
Meningococcus meningitis (N = 23)	9	1	2	1	2	0	1	0	3	4	0	0

TABLE 2. Results of CSF analysis and culture for 59 cases of bacterial meningitis.

Test	Value
Cells/HPF	1470 $\pm$ 302
Proteins (mg/L)	8101 $\pm$ 1780
Glucose (ng/L)	23.4 $\pm$ 1.33
Gram's stain (N = 40)	
Gram negative	34
Gram positive	6
Culture (N = 59)	
<i>Streptococcus pneumoniae</i>	7
Group B hemolytic streptococci	3
<i>Hemophilus influenzae</i>	21
<i>Neisseria meningitidis</i>	23
<i>Escherichia coli</i>	4
<i>Pseudomonas aeruginosa</i>	1

HPF = highpower field.

TABLE 3. The age factor in susceptibility to different organisms in meningitis.

Pathogen	Age group			Total
	< 1 yr (N = 34)	1-5 yr (N = 42)	> 5 yr (N = 30)	
<i>Streptococcus pneumoniae</i>	5	2	0	7
Group B hemolytic streptococcus	3	0	0	3
<i>Hemophilus influenzae</i>	11	8	2	21
<i>Neisseria meningitidis</i>	2	10	11	23
<i>Escherichia coli</i>	3	1	0	4
<i>Pseudomonas aeruginosa</i>	1	0	0	1
Viruses	8	10	7	25
Partially treated bacteria	10	15	10	35
Tuberculous bacilli	2	1	0	3

demonstrated organisms three times despite negative culture.

Blood culture was done in all patients. Thirty-three organisms were isolated and they corresponded to the CSF organisms. In two instances *N. meningitidis* was grown from blood but not from CSF.

Tubercular meningitis was diagnosed in three non-Saudi children. They were less than 2 years old, had been born at home, and had not had BCG

vaccination. They all showed a positive Mantoux reaction. One whose mother had been irregularly treated with antituberculosis drugs had miliary tuberculosis of the chest. The grandmother of the second patient had active tuberculosis. We could not document the disease in the family of the third patient.

The pattern of meningitis for different age groups is shown in Table 3.

All patients were treated in hospital with an average stay of 12 days. Main complications encountered in the short term were: 13 cases with cerebral palsy with or without convulsions, five with subdural effusion, and three with hydrocephalus. Four children died and the rest were discharged from the hospital in apparently normal health.

Discussion

Of the total annual admissions to our hospital, cases of meningitis constituted 3.2%. This is twice the annual rate seen at Riyadh Children Hospital [6] and triple that for the Central Hospital in the Eastern region [9]. In Kuwait, the central hospital has witnessed a mean annual incidence of 13.1/100,000 [17]. The increase in admissions for August (Table 1) corresponds to an increased incidence of group A meningococcus strain III-I [4] observed during the *Haj* period. Meningitis occurred throughout the year, including group A meningococcus, and mainly affected young children in the endogenous population. Cases were diagnosed early and the clinical presentation did not differ from that usually seen in this country.

We mainly depended on CSF culture to confirm the clinical diagnosis. As shown in Table 2, Gram's staining was helpful in 67.8% of cases, which is contrary to the report of Burans et al [15] who found Gram's staining superior to CSF culture in establishing diagnosis. Many factors influence the outcome of Gram's staining and the most important is the ability and reliability of the technician doing the test and the staining technique.

The latex test was done in a small number of patients but the results were good. This is similar to what has been reported by Girgis et al [16] who obtained 70% sensitivity for the latex test. Blood culture proved the least useful, though it was the only way to recover organisms in three patients.

Tuberculous meningitis continues to be diagnosed late. Despite a clinical suspicion, we could not confirm diagnosis by CSF, sputum, or gastric wash cultures. BCG vaccination prevents this disease and immunization coverage in this country is good. Still, some pockets of the disease need to be identified and reached.

As shown in Table 3, *H. influenzae* group B was the most common organism grown in patients under one year old (44%). This continues to be the case for patients during the first five years (46.3%), but *N. meningitidis* gradually begins to dominate. This pattern is similar to that reported by others for the region [8,11,17]. However, Babikir and Taha [6] found that *S. pneumoniae* was the most common isolate in the Riyadh population. Our 35.1% failure rate to isolate organisms from CSF despite contrary laboratory findings compares well with that in Riyadh (23%) [11] and Al-Khobar (34.8%) [8]. The complications encountered in the patients were expected ones [18] and bacterial meningitis remains a serious childhood problem [19,20].

Acknowledgment

We thank Dr. J. Kroshid and her colleagues in the Laboratory for their cooperation and help.

References

1. Vieusseux G. J Med Chir Pharm 1806;XI:163.
2. Noah ND. Epidemiology of bacterial meningitis—UK and U.S.A. In: Williams JD, Burnie J, eds. Bacterial meningitis. London: Academic, 1987.
3. Tikhomirov E. Meningococcal meningitis: global situation and control measures. World Health Stat Q 1987;40:98-108.
4. Moore PS, Reeves MW, Schwartz B, et al. International spread of an epidemic group A *Neisseria meningitidis* strain. Lancet 1989;2:260-2.
5. Bahemaka M, Babikir MA, Wright SG, et al. The pattern of infection of the nervous system in Riyadh: a review of 121 cases. Q J Med 1988;680:517-24.
6. Babikir MA, Taha SA. Meningitis in children in Riyadh. J Trop Med Hyg 1984;87:245-8.
7. Basrawi T. Meningitis in infants and children: hints, highlights, and signs of meningitis. Saudi Child 1981;2:2-9.
8. Abomelha A, Uduman SA, Saleh MF, et al. Childhood bacterial meningitis. Ann Saudi Med 1988;8:274-8.
9. Uduman SA, Abomelha A, Al-Fadel SM, et al. Childhood meningitis: a review of 161 cases over a three-year period in the Eastern Province of Saudi Arabia. Ann Saudi Med 1988;8:91A.
10. Mc Neil JR. Meningitis in Eastern Saudi Arabia: childhood meningitis. Med East Med J 1965;2:13-7.
11. Al-Moammar H, Mallouh A, Arrighi H, Abu-Osba Y. A five-year review of bacterial meningitis at Dhahran Health Centre. 8th Saudi Medical Conference. Riyadh, S.A., 1983;144.
12. Mc Neil JR. Acute bacterial meningitis as seen in children of Eastern Saudi Arabia. Clin Pediatr 1966;5:437-8.
13. Cheesbrough M, ed. Medical laboratory manual for tropical countries, Vol-II:30 ELBS. London: Butterworth, 1985.
14. Welcome Diagnostic ZL26, Dartford, England DAI 5AH. Issued February 1987.
15. Burans JP, El-Tayeb M, Abu-Elyazeed R, Woody JN. Comparison of latex agglutination with established bacteriological tests for diagnosis of cerebrospinal meningitis. Lancet 1989;2:158-9.
16. Girgis NI, Farid Z, Kilpatrick ME. Diagnosis of bacterial meningitis. Lancet 1989;2:1039.
17. Zaki M, Daoud AS, Al-Saleh Q. Childhood bacterial meningitis in Kuwait. Ann Saudi Med 1988;8:5.
18. Cogent B. Safety and efficacy of once-daily ceftriaxone for the treatment of bacterial meningitis. In: Percival A, ed. Insight into the treatment of serious infection. Proceedings of an international meeting in Basle, Switzerland, 1986;2(I):79-80.
19. Arditi M, Herold BC, Yogeu R. Cefuroxime treatment failure and *Haemophilus influenzae* case report and review of the literature. Pediatrics 1989;84(I):132-4.
20. Welsby PD, Golledge CL. Meningococcal meningitis (editorial). Br Med J 1990;300(6733):1150-1.

MEASLES VACCINE FAILURE

Ahmed Abanamy, MD; Mohammed Khalil, MPH, MSc;
Hussein Salman, MD; Mahmoud Abdulazeem, MSc

كان مستشفى الأطفال بالسليمانية في الرياض، بالمملكة العربية السعودية مركزاً للدراسة، ابتدأت في يونيو/ حزيران ١٩٨٧م واستغرقت عامًا واحدًا، تهدف إلى استقصاء الإخفاق في لقاح الحصبة. شمل القسم الأول من الدراسة ٣٣٦ مريضًا بالحصبة؛ تم التشخيص سريريًا، وأثبت بتحليل الغلوبولين المناعي (IgM) التآلقي. ضمت مجموعة الأطفال من ٩ شهور فما فوق، وهو السن القانوني للتلقيح، ٣١٠ حالات. بلغت نسبة الذين تم تلقيحهم ٢٩,٤٪، وهذه النسبة تبدو ضمن المدى السوي، مع الأخذ في الاعتبار نسبة التغطية المحلية للتلقيح ونسبة الانقلاب المصلي، مقارنة بمثيلاتها في البلدان الأخرى. كان السبب الرئيسي لفشل التلقيح هو استمرار أضداد الحصبة المكتسبة من الأم. أما الجزء الثاني من الدراسة فشمل اختبار فعالية بعض العينات من لقاح الحصبة التي تم الحصول عليها من مراكز صحية مختلفة في منطقة الرياض. وتبين موافقة فعاليتها للمستويات المطلوبة.

Suleimania Children's Hospital, Riyadh, Saudi Arabia was the site of a one-year study, started June 1987, which was designed to investigate measles vaccine failure. The first part of the study consisted of 336 patients with measles. Diagnosis was established on clinical grounds and confirmed by fluorescent IgM analysis. Those patients 9 months and older, which is the legal age of vaccination, comprised 310 subjects. Of these, 29.4% had been vaccinated. This percentage appears to be within the normal range, considering the local coverage rate of vaccination and seroconversion rate, compared with those for other countries. The main cause of vaccine failure was persistent maternal antibodies. The second part of the study involved testing the potency of some samples of measles vaccine obtained from various health centers in the Riyadh region. Potency was found to meet recommended standards.

During the past few years, many children with measles have been seen and treated at Suleimania Children's Hospital, many of whom had received the measles vaccination.

Vaccine failure can be classified as primary or secondary. In the primary form, there is failure to seroconvert and this is generally attributed to the neutralization of the attenuated virus by persistent maternal antibody in infants younger than twelve months old [1], to inadequate immunization due to improper storage conditions and/or handling of the vaccine [2,3], or to vaccination

administered in combination with immunoglobulin therapy [4-6].

In secondary vaccine failure, clinically apparent infection develops despite an immune response to vaccination [7-9]. However, this elicited response may not be adequate to protect against the subsequent inoculum of wild-type virus, or an initially protective response may wane over time. The presence of measles-specific immunoglobulin M (IgM) in the sera of patients with clinical measles infection has been used to differentiate a primary from secondary response [10-12].

The aim of this study was to determine the causes of vaccine failure in our community, as well as to propose a suitable age for measles vaccination and to evaluate the viability of the measles vaccine at the health centers.

From the Suleimania Children's Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Khalil: Suleimania Children's Hospital, P.O. Box 59046, Riyadh 11525, Saudi Arabia.

Accepted for publication 29 July 1990.

Material and Methods

First Part

All patients with measles who were admitted to Suleimania Children's Hospital or seen at the outpatient clinic from June 1987 to June 1988 were included in the study. A clinical diagnosis of measles was made if the patient had the following: (1) a generalized maculopapular rash that had lasted for three or more days; (2) temperature of 38.3°C or greater; and (3) either cough, coryza, or conjunctivitis [13]. The additional criteria of Koplik's spots and/or typical morbilliform rash were used so that cases seen earlier than the third day of rash could be included. One milliliter of blood was taken from each child for testing the presence of measles IgM. The serum was separated and stored at -20°C until testing. The measles IgM indirect fluorescent technique (IFT) was performed using standardized inoculum with Electronucleonic kits (Virgo, USA). Vaccination certificates were the source of the immunization status of the child.

Second Part

Forty-eight vaccine samples were collected from 24 health centers inside Riyadh city. Half were collected randomly during August 1987 and the remaining half during February 1988. The samples were transported in a standard fashion to the testing laboratory at Suleimania Children's Hospital. All vaccines were of the Schwartz strain (Rauvax Biomerieux). Assessment of viability was carried out using a tissue culture infective dose of 50% ICID₅₀. The end titer in vero cells was tested using growth and maintenance media microtiter plate technique. A TCID₅₀ of 10³ or over was considered usable according to manufacturer's recommendation [14].

Results

First Part

There were 336 cases of measles encountered during the study period; 173 were in males (51.5%) and 163 in females (48.5%). Patients 5 years and younger represented 71%; 23.7% were less than fifteen months of age, and 16.7% were less than one year. Twenty-six children (7.7%) were younger than 9 months, which is the legal age for measles vaccine. Children who were 1 to 3

years old represented the largest age group (N = 111; 33.0%). According to vaccination certificates, 91 (29.4%) of the 310 patients who were the legal age for vaccination had been vaccinated against measles. Of these, 73.6% had been vaccinated before twelve months of age and 26.4% at 15 months or older.

Fluorescent IgM tests were positive in 285 of the 304 patients tested (93.7%). Eighteen of the 19 IgM-negative samples were drawn before the third day of the rash, and this may have been too early to allow for accurate detection. In the remaining case, the sample was taken after the third day in a patient who had been vaccinated against measles. The IgM test was positive in 84 and negative in seven of the vaccinated children. The sample was taken on the first or second day of the rash in six of the IgM-negative patients.

Second Part

Of the 48 vaccine samples collected from Riyadh health centers, 46 met the recommended standard (titer of more than 1,000 TCID₅₀) [14]. The two remaining vials had a titer below this and had come from two different batches. The other vials from these two batches met the recommended standards.

Discussion

Vaccine failure is a known problem and has been observed since the introduction of measles vaccine in the Kingdom in 1983.

The present study shows measles infection still occurs mainly in the preschool age group, and the recent introduction of measles vaccination probably accounts for this.

Patients under nine months of age represented 7.7% of the total. The apparently low percentage in this age group should not be ignored, considering that it is expected to increase because of the higher vaccination coverage in the older group.

Vaccination certificates indicated that 29.4% of the measles patients had been vaccinated. The rate was 16.6% in similar studies done in Australia [15,16]. A difference in the legal age for vaccination could explain these different results. Most of our patients were vaccinated when younger than 12 months of age. The percentage of measles-vaccinated children in relation to the total number of

measles cases was 52% according to a survey done in the U.S.A. [17]. This high percentage was expected in the U.S.A. where a vaccination program was implemented a long time ago. In fact, the above percentage does not reflect the vaccine efficacy. Efficacy (VE) only can be calculated from the following equation [15,18]:

$$VE = \frac{\text{Unvaccinated attack rate} - \text{vaccinated attack rate}}{\text{Unvaccinated attack rate}}$$

From the above equation, and if the vaccine efficacy is known or if the seroconversion is used instead of vaccine efficacy, the percentage of the cases vaccinated can be calculated as follows [13]:

$$PCV = \frac{PPV - (PPV \times VE)}{1 - (PPV \times VE)}$$

where PPV represents the percentage of the population vaccinated.

In the Saudi community, where in 1987 the coverage rate was about 75%, and using the seroconversion rate of 85%, the PCV is 31%, a result equivalent to that in our study (29.4%). This implies that the percentage of measles cases among vaccinated children compared with the total number of measles cases in children is within the acceptable limit.

No difference was found in the IgM antibody response between vaccinated and nonvaccinated children with measles. This primary immunological response indicates a primary vaccine failure [8].

Regarding the age of immunization, 73.6% of our patients were younger than 15 months of age when vaccinated. In this group, the vaccine failure is mainly due to persistent maternal antibodies. Twenty-six percent of the patients were vaccinated after fifteen months of age, and all except one had an IgM antibody response. This could be related to a possible cold chain defect at the time or lack of actual vaccination. The single patient who was vaccinated when older than fifteen months and who had no IgM antibody response had been immunized since the age of 4 years and 10 months. This probably represents a secondary vaccine failure [7,8]. Our study therefore shows that the main cause of vaccine failure is primary failure due to persistent maternal antibodies and cold chain defect.

Three factors must be considered when determining the earliest feasible age for vaccination: the time when maternal antibodies wane, the incidence rate of measles infection in the first months of life, and the efficacy of vaccination before twelve months of age.

The optimum age for measles vaccination is still a controversial issue. Fixing the age of vaccination at nine months is not suitable considering the presence of maternal antibodies and the doubts about vaccine efficacy before twelve months of age. Therefore, we recommend deferring the legal age of vaccination to at least twelve months. However, in developing countries and in those where vaccination has only recently been introduced, the incidence of measles is higher in the first few months of life, with increased risk of severe complications. The Advisory Committee on Immunization of Practices and the American Academy of Pediatrics have recommended that infants as young as 6 months should be immunized when exposure to measles is considered likely. This should be followed by reimmunization at fifteen months of age to ensure protection.

In Saudi Arabia, where measles vaccination was only recently introduced in 1983, earlier immunization at 6 months in the Saudi community should be adopted along with compulsory revaccination at 15 months. The use of the Edmonston-Zagreb strain can also be considered [19]. Later, after periodic epidemiological evaluation of the measles infection in the Saudi community, the recommended age for measles vaccination can be re-evaluated. The cold chain should also be monitored periodically, especially at the health center level, to ensure consistent quality.

References

1. Yeager AS, Davis VH, Ross LA, et al. Measles immunization successes and failures. *JAMA* 1977;237:347-51.
2. Albrecht P, Ennis FA, Saltzman FH, et al. Persistence of maternal antibody beyond twelve months, mechanisms of measles vaccine failures. *J Pediatr* 1977;91:715-9.
3. Sato H, Albrecht P, Reynolds DW, et al. Transfer of measles, mumps, and rubella antibodies from mother to infant, its effect on measles, mumps, and rubella immunization. *Am J Dis Child* 1979;133:1240-3.
4. Lerman SJ, Gold E. Measles in children previously vaccinated against measles. *JAMA* 1971;215:1311-5.
5. Baratta RD, Genter MC, Price MA, et al. Measles (rubeola) in previously immunized children. *Pediatrics* 1970;46:379-402.

6. Arbeter AM, Arthur JH, Blakeman GJ, et al. Measles immunity: re-immunization of children who previously received live measles vaccine and gamma globulin. *J Pediatr* 1973;81:737-41.
7. Cherry JD, Feigin RD, Stockel Ford PG, et al. A clinical and serological study of 103 children with measles vaccine failure. *J Pediatr* 1973;82:802-8.
8. Linnemann CC, Hegg ME, Botte TC, et al. Measles IgM response during reinfection of previously vaccinated children. *J Pediatr* 1973;82:798-801.
9. Deseda-Tous J, Cherry JD, Spencer MG, et al. Measles revaccination: persistence and degree of antibody titer by type of immune response. *Am J Dis Child* 1978;132:287-90.
10. Schluederberg A. Immunoglobulin in human vitamin infection. *Nature* 1965;205:1232.
11. Schluederberg A. Modification of immunoresponse by previous experience with measles. *Arch Gesamte Virusforsch* 1965;16:347.
12. Heffner RR, Schluederberg A. Specificity of the primary and secondary antibody response to myxoviruses. *J Immunol* 1967;98:668-72.
13. Centers for Disease Control. Classification of measles cases. *MMWR* 1983;31:707-11.
14. Wegmann PA, et al. Further attenuated live measles vaccine. *Dev Biol Stand* 1985;65:69-74.
15. Christopher RJ, MacDonald PA, Murphy AM, Buckley PR. Measles in the 1980s. *Med J Aust* 1983;2:488-91.
16. Feery B. Impact of immunization on disease patterns in Australia. *Med J Aust* 1981;2:172-6.
17. Centers for Disease Control. Measles vaccine efficacy. United States (editorial). *MMWR* 1980;29/30:470-2.
18. Aaby P, Bukh J, Leerhoy J, et al. Vaccinated children get milder measles infection. A community study from Guinea-Bissau. *J Infect* 1986;154(5):858-63.
19. Markowitz LE. Immunization of young infants with Edmonston-Zagreb measles vaccine. *Pediatr Infect Dis* 1987;5,6:809-12.

MANTOUX REACTION SURVEY CONDUCTED IN THE NORTHERN REGION OF SAUDI ARABIA

Feisal Al-Kassimi, MRCP; Anwar Abdullah, FRCPC;
Ibrahim Al-Orainey, MRCP; Mohamed Al-Hajjaj, FRCPC;
Essam Al-Deen Abdul Baghee, MBBCh; Abdul-Baree Baner, PhD

يجري حالياً مسح وبائي يشمل القطر كله لتقويم انتشار خمج السل بين سكان المملكة العربية السعودية. ومن وسائل التقويم اختبار (مانتو) وزرع عينات القشع المأخوذة من قاطني مناطق المملكة الخمس. وقد اختيرت جبهة الدراسة باستخدام طريقة تناسبية لعدد السكان مع اعتيان عنقودي وتطقي ريفي / حضري. وتتم هذه الدراسة بنتائج اختبار (مانتو) في المنطقة الشمالية حيث تم الكشف على ألف وثلاثمائة وأربعين شخصاً. أظهر ٤٪ فقط من الأطفال الذين لم يتلقوا لقاح بي سي جي تفاعلاً إيجابياً (منسب السل) الأمر الذي يعني أن المنطقة ذات انتشار متوسط (٢ - ١٤٪) ويشير إلى الحاجة إلى اعتماد وسائل أفضل لكشف حالات السل المفتوح في المجتمع ومعالجتها. ارتفع منسب السل ارتفاعاً حاداً مع السن إلى نسبة ٥٨٪ لدى من كانت أعمارهم ٦٥ عاماً فما فوق، الأمر الذي يدل على وجود مجموعة كبيرة من الأصحاء المخموجين والمعرضين لتنشط المرض. كان منسب التدرن أعلى لدى الذكور والممارسين لأعمال يدوية، بيد أنه لم يكن للجنسية، (سعودي أو غير سعودي)، ولا لمكان الإقامة أو مستوى التعليم أية دلالات إحصائية. تساند نتائجنا هذه وجهة النظر القائلة بأن التفاعل الإيجابي للسليين لدى الأطفال بين سن الخامسة والرابعة عشرة تلقوا لقاح بي سي جي يجب أن يعزى إلى الخمج بالمتفطرة السلية وليس إلى لقاح بي سي جي. وقد خلصنا إلى ذلك بناءً على ما وجدناه من أن نسبة ٥٪ فقط من الأطفال في المجموعة التي تلقت لقاح بي سي جي أظهرت تفاعل (مانتو) إيجابياً، بينما أظهرت نسبة ٥٪ تفاعلاً متوسطاً (٥ إلى ٩ ملم تصلب) وكان التفاعل سلبياً لدى نسبة ٩٠٪ (صفر إلى ٤ ملم تصلب).

A nationwide epidemiological survey is under way to assess the prevalence of tuberculosis infection in the inhabitants of Saudi Arabia. The assessment tools include the Mantoux test and culturing of sputum samples obtained from inhabitants of the five regions of the Kingdom. The study population has been selected using a proportional-to-population-size method with cluster sampling and urban/rural stratification. We report the results of the Mantoux test for the Northern Region, where 1340 subjects were screened. Only 4% of the non-BCG-vaccinated children had a positive reaction (tuberculosis index = TI) which identifies the region as a middle prevalence country (2-14%), and indicates the need for better

From the Medical Department, College of Medicine, King Saud University (Drs. Al-Kassimi, Al-Orainey, Al-Hajjaj), Riyadh; Hamad Hospital (Dr. Abdullah), Al-Doha, Qatar; Medical Services, Al-Imam Mohamed Bin-Saud Islamic University (Dr. Baghee), Riyadh; College of Science, Kuwait University (Dr. Baner), Kuwait.

Address reprint requests and correspondence to Dr. Al-Kassimi: Medical Department, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Accepted for publication 18 July 1990.

detection and treatment of open cases of tuberculosis in the community. The TI rose steeply with age to 58% in the 65+-year age group, which denotes the existence of a large pool of infected but healthy subjects who are liable to suffer active disease. The TI was higher in males and in those doing manual work, but was not statistically influenced by nationality (Saudis versus non-Saudis), place of residence, or level of education. Our findings support the view that a positive tuberculin reaction in a child aged 5 to 14 years who has been vaccinated with bacillus Calmette-Guerin (BCG) should be attributed to infection with *Mycobacterium tuberculosis* and not BCG. This conclusion is based on our finding that only 5% of the children in the group of vaccinated subjects had a positive Mantoux reaction, 5% had an intermediate reaction (5 to 9 mm induration), and 90% had a negative reaction (0 to 4 mm induration).

King Abdul Aziz City for Science and Technology in Riyadh, Saudi Arabia, has sponsored a nationwide epidemiological survey to determine the prevalence of tuberculosis in Saudi Arabia. Although tuberculosis is a serious health problem in Saudi Arabia [1-3], the country still does not have a reliable notification system for recording active cases, nor have comprehensive epidemiological studies been conducted. The survey has been designed to determine the prevalence of tuberculosis infection using the age-specific Mantoux test as well as the extent of open (and hence infectious) cases in the community through sputum culture for mycobacteria. These indices were considered by a WHO Expert Committee on Tuberculosis in 1974 to be the most accurate for assessing the tuberculosis problem in a community [4]. The present paper reports the results of the Mantoux test in the Northern Region of Saudi Arabia and their correlation with various sociodemographic factors. The results of the Mantoux test from other regions and sputum studies, which are still under way, will be reported later.

Previous tuberculin skin test studies done in the Kingdom have yielded conflicting results, with positive rates as high as 70% and as low as 1.9% [1]. This is not surprising given the small number of subjects included, the biased selection of the subjects [5], and the lack of standard procedures, as one study used the tine test [5] while another used the Mantoux [6].

Material and Methods

The towns of Qassim, Hail, Tabuk, and Sakakah and their rural outskirts were selected by a proportional-to-population-size method with cluster sampling and urban/rural stratification. According to the last available census, the population of the Emirates of the Northern Region was

1,003,800, of whom approximately 40% lived in urban areas. The target of the national survey was to screen 1/750 to 1/1000 of the population. Accordingly, a sample of 1340 subjects was considered proportionate to the Northern Region. A total of 19 urban and 27 rural clusters was randomly selected. Each cluster contained 30 to 40 clusters, maintaining an urban-to-rural ratio of 4 to 6. Children younger than 5 years were excluded, as it was not practical to administer the Mantoux test to them. Attempts in a pilot study had shown poor compliance rates that would have jeopardized the accuracy of the survey.

Administration of the Mantoux test and collection of data were performed by a specially trained field team consisting of one physician and two nurses. Using a pre-designed questionnaire, the following information was recorded: age, nationality (Saudi or non-Saudi); education (none, primary, secondary, higher); occupation—sedentary (professional, clerical, salesman), manual, student, not working (including housewives); and history of previous bacillus Calmette-Guerin (BCG) vaccination and the presence of a BCG scar. Medical history was also obtained regarding the presence of fever or cough for longer than one month as well as past history or family history of tuberculosis. Each subject (5 years or older) was given 5 units of tuberculin intradermally [7] in the form of purified protein derivative (PPD) mixed with Tween 80, and injected on the volar aspect of the forearm. The test was read 48 hours later. An induration of at least 10 mm was considered positive [7]; 5 to 9 mm was considered intermediate, and 0 to 4 mm was interpreted as a negative reaction.

The correlation between the various population characteristics and Mantoux reaction was evaluated by F-test (two-way ANOVA) using "Epistat" version 3.2 [8]. $P < 0.05$ was considered significant.

TABLE 1. *Characteristics of the population surveyed.*

Characteristics	Number
Total no. interviewed	1340 (100%)
Age (yr)	
5-14	593 (44%)
15-24	342 (25.5%)
25-34	127 (9.4%)
35-44	111 (8.2%)
45-64	130 (9.7%)
65+	37 (2.8%)
Sex	
Male	537 (40.1%)
Female	803 (59.9%)
Residence	
Urban	520 (38.8%)
Rural	820 (61.2%)
Nationality	
Saudi	1287 (96%)
Non-Saudi	53 (4%)
Education	
None	487 (36.4%)
Primary	645 (48.1%)
Secondary	181 (13.5%)
Higher	27 (2.0%)
Occupation	
Sedentary	106 (7.9%)
Manual	102 (7.6%)
Students	717 (53.5%)
Not working (including housewives)	415 (31.0%)
BCG history	
Positive	671 (50.0%)
Negative	669 (50.0%)

Results

Characteristics of the Population Surveyed

Table 1 summarizes the characteristics of the population surveyed. The accuracy of the BCG history was confirmed by its high correlation with the presence of a BCG scar, and this was seen in 98% of the 671 subjects who claimed receiving the vaccine.

Effect of Age and Previous BCG Vaccination on Mantoux Reaction

Table 2 and Figure 1 illustrate the association of age and previous BCG history with the Mantoux reaction. An intermediate reaction (5-9 mm induration) was consistently seen in less than 10% of the overall population and was not influenced by previous BCG vaccination ($P > 0.3$) or age ($P > 0.6$). However, a positive Mantoux reaction (≥ 10 mm induration) was seen in significantly more BCG-vaccinated subjects ($P = 0.026$) and in older age groups ($P = 0.0045$). The statistically significant difference between the vaccinated and unvaccinated group was manifest only in adults; unvaccinated children, aged 5 to 14 years, had a 4% positive Mantoux rate as opposed to 5% in the vaccinated group. The overall prevalence of a positive Mantoux reaction in the unvaccinated group was 19% and reached its peak (58%) in the 65+ age group.

Effect of Sociodemographic Factors on the Prevalence of Positive Mantoux Test in BCG-unvaccinated Subjects

The population characteristics with regard to the Mantoux test in BCG-unvaccinated subjects are outlined in Table 3. The overall rate of positivity in males was 37%, which was significantly

TABLE 2. *Mantoux reaction size according to BCG history and age.*

Mantoux reaction size	BCG history	Age (yr)						P value	
		5-14	15-24	25-34	35-44	45-64	65+	Row	Column
5-9 mm	Negative	4/194 (2%)	0/149	3/70 (4%)	4/99 (4%)	10/121 (8%)	2/36 (6%)	> 0.3 (NS)	> 0.6 (NS)
	Positive	17/399 (4%)	27/193 (14%)	5/57 (9%)	0/12	1/9 (11%)	0/1		
10 + mm	Negative	7/194 (4%)	10/149 (7%)	13/70 (19%)	27/99 (27%)	46/121 (38%)	21/36 (58%)	.026	.0045
	Positive	21/399 (5%)	41/193 (21%)	18/57 (32%)	5/12 (42%)	5/9 (56%)	1/1 (100%)		

TABLE 3. Prevalence of positive (10 mm+) Mantoux reaction according to characteristics.

Characteristics	Age (yr)						Pvalue
	5–14	15–24	25–34	35–44	45–64	65+	
Sex							
Male	4/55 (7%)	3/20 (15%)	6/11 (55%)	10/23 (43%)	27/53 (51%)	18/25 (72%)	0.01
Female	3/139 (2%)	7/129 (5%)	7/59 (12%)	17/76 (22%)	19/68 (28%)	3/11 (27%)	
Residence							
Urban	3/71 (4%)	4/62 (6%)	7/33 (21%)	12/41 (29%)	15/39 (38%)	8/58 (14%)	0.2 (NS)
Rural	4/123 (3%)	6/87 (7%)	6/37 (16%)	15/58 (26%)	31/82 (38%)	13/22 (59%)	

NS = not significant.

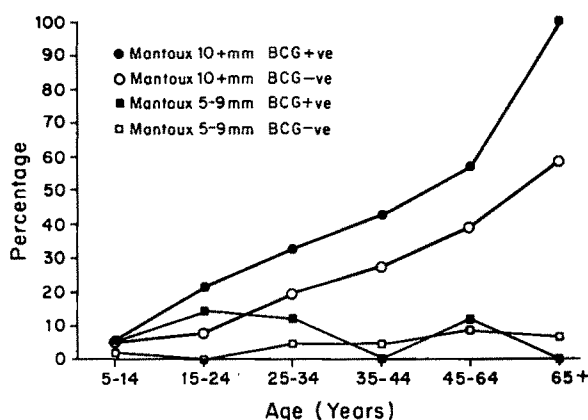


FIGURE 1. Effect of age and previous BCG vaccination on Mantoux reaction.

higher ($P < 0.01$) than that in women (12%). The difference was more marked in the 25-34 year age group (55% versus 12% in females).

There was no statistically significant difference observed for study subjects living in urban and rural communities ($P > 0.2$). Although Saudis had lower rates than non-Saudis (18 versus 22%), the difference was not statistically significant ($P > 0.06$). The number for non-Saudis was really too small ($N = 86$), however, to allow for meaningful comparisons.

The level of education was not significantly associated with the rate of positivity ($P = 0.00323$).

The prevalence of positive Mantoux reactions was not significantly influenced by history of cough ($P > 0.04$), expectoration ($P > 0.5$), fever ($P > 0.05$), history of other chest disease ($P > 0.1$), or family history of tuberculosis ($P > 0.5$). The number of subjects with a past history of

tuberculosis was too small to allow for meaningful statistical analysis.

Discussion

This study revealed that only 4% of unvaccinated children, aged 5 to 14 years, had a positive Mantoux reaction (TI). The higher proportion of children in the 5 to 14 year age group (see Table 1) does not probably represent biased selection, but is indicative of the large number of children in Saudi families and the improved survival of the new generation. To our knowledge, there are no published data on the age distribution of the Saudi population that would clarify this finding.

Applying the classification proposed by the International Union against Tuberculosis [9], the Northern Region of Saudi Arabia ranks with the middle prevalence countries (2-14%). Table 4 compares our findings with those reported for other countries, though it must be borne in mind that the tuberculin dose and criteria for a positive reaction varied among studies. Although low by third world standards, the tuberculosis index (TI) in our study indicates that children are still liable to come in contact with open cases of tuberculosis at a rate higher than that for children in developed countries, where less than 2% of the children are tuberculin reactors [10]. The current policy of supplying medical care and antituberculous drugs free of charge should be continued. Compulsory screening of subjects who have been in contact with active cases must be strongly considered.

The lower TI in females than males agrees with that reported from previous studies from other third world countries [11]. The TI in our study was

TABLE 4. Prevalence of tuberculosis infection rate reported from some other countries compared with the findings in the current study.

Country	Year	Age	Tuberculin dose	Criterion for positive reaction	Prevalence	Study
India (rural)	1968	5-14	1 unit	10 mm	15.4%	[11]
Edinburgh (Caucasians)	1979	5-14	Heaf rest	Reaction grade III or IV	0%	[24]
South Africa	1974-1980	10-14	2 units	10 mm	-	[35]
Whites					2.3%	
Asians					5.5%	
Blacks					21.4%	
Gambia (rural)	1985	10	5 units	> 10 mm	20.0%	[27]
Current study	1989	5-14	5 units	10 mm	4%	-

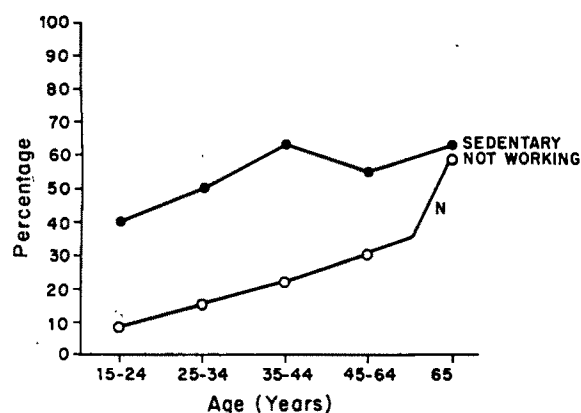


FIGURE 2. Effect of occupation on positive Mantoux reaction (BCG-negative subjects).

more marked in the 25 to 34-year age group, which coincides with peak years of social mobility for young men as opposed to women who spend most of their time at home. The lack of a significant difference between urban and rural findings and between Saudis and non-Saudis can be attributed to the fact that the Northern Region does not contain large metropolitan centers where foreign laborers of low socioeconomic background tend to congregate. This view is supported by results from the Western Region where the same survey has been conducted. Large foci of significantly higher TIs were found in urban non-Saudis in Jeddah [12]. However, as mentioned in the Results section, the lack of significant differences on the basis of nationality might represent a technical bias introduced by the small number of

non-Saudis in the study. The difference between subjects employed in sedentary occupations and those not working is probably a sex bias, as most of the latter category consist of housewives (Figure 2). Lastly, the absence of correlation with respiratory symptoms is not surprising, given the fact that the majority of tubercular infections remain subclinical.

The steep rise of TI in the 25 to 34-year age group (Table 2, Figure 1), particularly in males (Table 3, Figure 3), denotes the presence of a large pool of infected subjects in the community who are at some risk for active disease. Prophylaxis with isoniazid for high-risk groups [13], like subjects receiving long-term corticosteroids, should therefore have a considerable impact on the incidence of active cases in Saudi Arabia. The steep rise at age 25 to 34 is probably multifactorial. The opportunity to acquire infection is increased when young adults leave home to seek education or employment, and this could explain why the rise was more steep in men than women. The higher TI for this age group might also result from a higher infection risk for people born in decades when fewer local facilities existed for the treatment of open cases of tuberculosis.

From our findings we are able to make recommendations regarding BCG vaccination in the region. Although no guarantee of successful vaccination, a visible scar from BCG vaccination usually indicates immunity [14]. It is reassuring that 98% of those who said they were vaccinated had a visible scar, which indicates that the techniques of BCG vaccination practiced in the region are prob-

ably sound. However, it is alarming that 32% (194/593) (Table 2) of the children aged 5 to 14 in our survey had not received BCG vaccine even though vaccination at birth is compulsory. The results of our study vindicate the current policy of BCG vaccination, as the WHO Expert Committee on Tuberculosis [15] recommends continuing early life vaccination until the percentage of tuberculin reactors drops to 2% at school entering age (i.e., low prevalence levels). It might also be advisable, in conformity with WHO recommendations [15], to revaccinate all children when they leave school, without repeat tuberculin testing. This view is strengthened by our finding a steep rise in the TI in the 25 to 34-year age group, and the fact that the protective effect of BCG vaccination does not last beyond ten years [16,17].

Use of the Mantoux test in a clinical setting is widely recommended for the diagnosis of tuberculosis [18]. However, interpretation of a positive test in a child who has recently received BCG vaccine poses considerable difficulty [18–20], as the reaction might represent either the effect of BCG or actual infection with *M. tuberculosis*. Evidence in the literature is conflicting, as some studies found that the effect of BCG on tuberculin skin sensitivity wanes in a few years [21–24], while others found it persists for a long time [25–27]. The discrepancy in results may reflect the fact that various BCG strains differ in their ability to induce skin sensitivity [14,26,28], which does not correlate with the protective effect of the vaccine [28–30]. In our study, 4% of BCG-negative children aged 5 to 14 years were Mantoux positive as opposed to 5% of BCG-positive children. This finding supports the previously expressed opinion that a child with a positive Mantoux reaction should be considered infected with *M. tuberculosis* regardless of his vaccination status [18]. Accordingly, isoniazid prophylaxis should be considered for all persons younger than 35 years who have a positive Mantoux reaction, as recommended by the American Thoracic Society [18].

Intermediate Mantoux reactions (5–9 mm induration) remained consistently below 10% (Table 2, Figure 1) and were not affected by previous BCG vaccination ($P > 0.3$) or age ($P > 0.6$). The failure to increase with age rules out the likelihood that an intermediate reaction represents infection with *M. tuberculosis*. Studies in North America

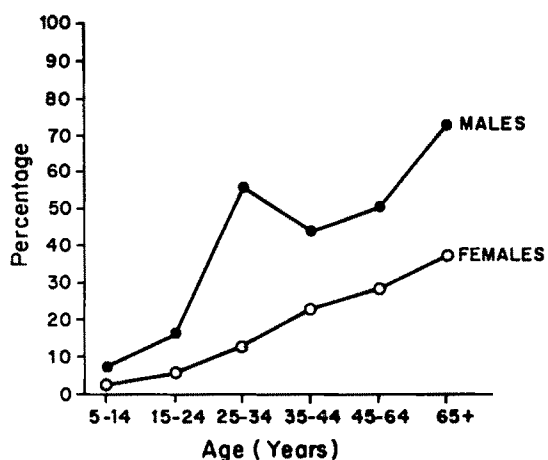


FIGURE 3. Effect of sex on positive Mantoux reaction (BCG-negative subjects).

have shown that intermediate skin reaction to tuberculin is common in subjects who had displayed a positive reaction to antigens prepared from atypical mycobacteria [31,32]. As these organisms are ubiquitous in nature [33,34], sensitization to them occurs at a young age, which would explain the lack of rise of incidence of an intermediate Mantoux reaction in our study.

In conclusion, the TI in children was 4%, which implies an intermediate prevalence of tuberculous infection, and this calls for increased efforts to treat open cases which are the source of infection in the community. The rise with age was more dramatic and steep in males than females, which is probably related to social reasons. We found a large pool of subjects with inactive tuberculous infection who might benefit, in selected cases, from prophylaxis with isoniazid. The current policy of giving BCG vaccine at birth should be continued, as the TI is still above 2% in children; revaccination when children leave school should be considered in view of the steep rise seen in the 15 to 25-year age group. Tuberculin skin sensitivity induced by BCG wanes in children 5 years after vaccination, and a positive reaction should be interpreted to represent infection with *M. tuberculosis*.

Acknowledgment

The project was supported financially by KACST (King Abdul Aziz City for Science and Technology)—Grant No. AT-8-113.

References

1. Sebai ZH. Health in Saudi Arabia, Volume 2. Riyadh, Saudi Arabia: Directorate of Scientific Research—King Abdul Aziz City for Science and Technology, 1987;30-1.
2. Sebai ZA. The health of the family in changing Arabia. Jeddah: Tihama Publications, 1981;93, 100, 127.
3. Shanks NJ, Khalifa I, Al-Kalai D. Tuberculosis in Saudi Arabia. *Saudi Med J* 1983;4:151-6.
4. WHO Expert Committee on Tuberculosis. Ninth Report. WHO Technical Report Series: No. 522. Geneva: WHO, 1974;7.
5. Rowlands DF. Tuberculin sensitivity in a Saudi military school population. *Saudi Med J* 1984;5:183-9.
6. Grimes J, Sparrow JY, Woodbine A. Program of health education and health screening in schools. *Saudi Child* 1980;1:22-8.
7. American Thoracic Society. Diagnostic standards and classification of tuberculosis and other mycobacteriae diseases, ed 14. *Am Rev Respir Dis* 1981;123:343-58.
8. Gustafson TL. Epistat—statistical package for the IBM PC, Version 3.2, 1985. Round Rock, Texas, U.S.A.
9. Tuberculosis Association of India, eds. Textbook of Tuberculosis. New Delhi: Vikas Publishing House, 1981;63-4.
10. U.S. Department of Health, Education and Welfare. Tuberculosis Programs, 1973. (Public Health Service, Publication No. CDC 75-8189) December, 1974.
11. National Tuberculosis Institute, Bangalore. Tuberculosis in a rural population of South India: a five-year epidemiological study. *Bull WHO* 1974;51:473-88.
12. Al-Kassimi FA, Abdullah AK, Al-Hajjaj MS, Al-Orainey IO. Tuberculosis epidemiology in the western region of Saudi Arabia—Proceedings of the British Society. *Thorax* 1989;44:869.
13. Weg JC. Chronic respiratory tract infections. In: Guenter CA, Welch MH, eds. *Pulmonary Medicine*, ed 2. Philadelphia: Lippincott, 1982;419-20.
14. Vallishayee RS, Shashidhara AN, Bunch-Christensen K, Guld J. Tuberculin sensitivity and skin lesions in children after vaccination with 11 different BCG strains. *Bull WHO* 1974;51:489-94.
15. WHO Expert Committee on Tuberculosis. (WHO Technical Report Series, No. 290). Geneva: WHO, 1964;10.
16. Tverdal A, Funnemark E. Protective effect of BCG vaccination in Norway 1958-73. *Tubercle* 1988;69:119-23.
17. D'arcy Hart P, Sutherland I. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early life—final report to the Medical Research Council. *Br Med J* 1977;2:293-5.
18. American Thoracic Society. The tuberculin skin test—official ATS statement. *Am Rev Respir Dis* 1981;124:356-63.
19. Farer LS. Prior BCG vaccination and PPD skin test. *JAMA* 1983;250:3106.
20. Snider DE. Bacille Calmette-Guérin vaccinations and tuberculin skin test—commentary. *JAMA* 1985;253:3438-9.
21. Bahr GM, Stanford JL, Rook GAW, et al. Two potential improvements to BCG and their effect on skin test reactivity in Lebanon. *Tubercle* 1986;67:205-18.
22. Fox AS, Lepow ML. Tuberculin skin testing in Vietnamese refugees with a history of BCG vaccination. *Am J Dis Child* 1983;137:1093-4.
23. Comstock GW, Edwards LB, Nabangxang H. Tuberculin sensitivity eight to fifteen years after BCG vaccination. *Am Rev Respir Dis* 1971;103:572-5.
24. Capewell S, Gordon Leitch A. Tuberculin reactivity in a chest clinic: the effects of age and prior BCG vaccination. *Br J Dis Chest* 1986;80:37-44.
25. Guld J, Wadler H, Sundaresan TK, et al. The duration of BCG-induced tuberculin sensitivity in children, and its irrelevance for revaccination. *BULL WHO* 1968;39:829-36.
26. Horwitz O, Bunch-Christensen K. Correlation between tuberculin sensitivity after 2 months and 5 years among BCG vaccinated subjects. *Bull WHO* 1972;47:49-58.
27. Elliott A, Bradley AK, Tulloch S, Greenwood BM. Tuberculin sensitivity in rural Gambian children. *Ann Trop Paediatr* 1985;5:185-9.
28. Comstock GW. Identification of an effective vaccine against tuberculosis. *Am Rev Respir Dis* 1988;238:479-80.
29. D'Arcy Hart P, Sutherland I, Thomas J. The immunity conferred by effective BCG and vole bacillus vaccines, in relation to individual variations in induced tuberculin sensitivity and to technical variations in the vaccines. *Tubercle* 1967;48:201-10.
30. Comstock GW. Vaccination against tuberculosis: controlled trials of BCG vaccination by the U.S. Public Health Service. Proceedings of the International Conference on the Application of Vaccines against Viral, Rickettsial and Bacterial Diseases of Man, 1971. *PAHO Sci Publ* 226;378-81.
31. Snider DE. The tuberculin skin test. *Am Rev Respir Dis* 1982;125 part 2:108-18.
32. Gryzbowski S, Brown MT, Rowe JF. Significance of the tuberculin reaction. *Can Med Assoc J* 1969;100:984-7.
33. Falkinham JO, Parker BC, Gruft H. Epidemiology of infection by non-tuberculous mycobacteria: I. Geographic distribution in the Eastern United States. *Am Rev Respir Dis* 1980;121:931-7.
34. George KL, Parker BC, Gruft H, Falkinham JO. Epidemiology of infection by non-tuberculous mycobacteria: II. Growth and survival in natural waters. *Am Rev Respir Dis* 1980;122:89-94.
35. Fourie PB. The prevalence and annual rate of tuberculous infection in South Africa. *Tubercle* 1983;64:181-92.

URINARY TRACT INFECTION IN PREGNANCY

Hassan Abduljabbar, MD, FRCS(C); Rajaa A. Moumena, BSC;
Hisham A. Mosli, FRCS(C); Ahmed S. Khan, MRCP(Ireland);
Ahmed Warda, MD, PhD

أخذت عينات أوسط جريان البول من ٢٦٤٢ حاملا لدى أول مراجعة للعناية بالحامل وذلك خلال الفترة من يناير ١٩٨٧م إلى يناير ١٩٨٨م. كان الغرض من أخذ هذه العينات دراسة الأحياء المجهرية فيها. وجدت بيلة جرثومية هامة لدى ما نسبته ٨,١٥٪ (العدد = ٤١٩): لم تظهر أعراض على ١٨٨ مريضة وظهرت لدى ٢٣١ مريضة، فكانت نسبة الوقوع ١,٧٪ و ٨,٧٪ على التوالي. واختيرت مئتا امرأة ممن كانت مزارع البول لديهم سلبية ليشكلن مجموعة ضابطة متوافقة من ناحية السن وعدد مرات الحمل وعمر الحمل، ووجد أن تواتر حدوث الولادة المبكرة أعلى في المجموعة العرضية فقط (P أقل من ٠,٠٥) في حين كان تواتر فقر الدم وفرط ضغط الدم وداء السكري أعلى في المجموعتين العرضية واللاعرضية بالمقارنة مع المجموعة الضابطة (P أقل من ٠,٠٥).

During the period January 1987 until January 1988, midstream urine specimens were collected during the first antenatal visit of 2,642 pregnant patients. The specimens were obtained for the purpose of microbiological study. Significant bacteriuria was found in 15.8% ($N = 419$); 188 of the patients were asymptomatic and 231 were symptomatic, yielding an incidence of 7.1% and 8.7%, respectively. Two hundred females with negative urine cultures were selected as a control group, and matched by age, gravidity, and gestational age. The frequency of occurrence of premature birth was found to be higher only in the symptomatic group ($P < 0.05$), while the frequency of anemia, hypertension, and diabetes was found to be higher in both symptomatic and asymptomatic patients, compared with the control group ($P < 0.05$).

Urinary tract infections (UTIs) are second in frequency only to respiratory tract infections in the general practice of medicine [1]. Females are more prone than males to UTIs, and this tendency seems to increase during pregnancy. This increased predisposition to UTIs during pregnancy is partly the result of the pressure of the gravid uterus on the ureters causing stasis of urine flow and is also attributed to the hormonal and

immunological changes that occur during normal pregnancy [1].

We report on a study carried out at King Abdulaziz University Hospital, Jeddah, that was designed to determine the frequency of significant bacteriuria in healthy pregnant females and its impact on pregnancy.

Material and Methods

In a prospective study conducted over a one-year period from 1987 to 1988, midstream urine samples were collected from 2642 pregnant females who had no apparent underlying medical ailments. All patients were attending the antenatal clinic at King Abdulaziz University Hospital, Jeddah. The urine samples were col-

From the Departments of Obstetrics/Gynecology, Microbiology, Urology, and Medicine, King Abdulaziz University, College of Medicine, Jeddah.

Address reprint requests and correspondence to Dr. Abduljabbar: Department of Obstetrics and Gynecology, King Abdulaziz University Hospital, P.O. Box 6615, Jeddah 21452, Saudi Arabia.

Accepted for publication 29 July 1990.

TABLE 1. Mean $\pm$ standard deviation of age and gravidity in the three groups.

	Control group	Asymptomatic group	Symptomatic group
Age (yr)	26.35 $\pm$ 4.83	26.37 $\pm$ 4.85 ^a	26.41 $\pm$ 4.82 ^a
Gravidity	4.34 $\pm$ 2.27	4.38 $\pm$ 2.14 ^a	4.33 $\pm$ 2.23 ^a
Gestational age (wk)	15.00 $\pm$ 1.50	14.50 $\pm$ 1.00 ^a	14.00 $\pm$ 2.00 ^a

^aNot significant.

TABLE 2. Frequency of complications in symptomatic bacteriuric pregnant patients.

Complication	Symptomatic bacteriuric (N = 231)	Control group (N = 200)	P value
Premature birth	30(13.0%)	16(8.0%)	< 0.05
Diabetes	15(6.5%)	6(3.0%)	< 0.05
Hypertension	19(8.2%)	8(4.0%)	< 0.05
Anemia	21(9.1%)	9(4.5%)	< 0.05

TABLE 3. Frequency of complications in asymptomatic bacteriuric pregnant patients.

Complication	Asymptomatic bacteriuric (N = 188)	Control group (N = 200)	P value
Premature birth	18(9.6%)	16(8.0%)	Not significant
Diabetes	13(6.9%)	6(3.0%)	< 0.05
Hypertension	16(8.5%)	8(4.0%)	< 0.05
Anemia	17(9.0%)	9(4.5%)	< 0.05

lected under supervision, using proper aseptic precautions, and were cultured using the Dip Strip technique [2]. Colonies were identified using standard methods [3]. Gram-negative bacilli were identified using the AP120E system.

Subjects who were found to have significant bacteriuria (i.e., those with a bacterial count over 100,000 organisms per milliliter in a fresh "clean catch" urine specimen [4]) were divided into two groups: those with asymptomatic bacteriuria, and those with symptoms of UTI (i.e., cystitis and/or pyelonephritis). All patients were monitored, as were 200 pregnant subjects with a negative urine culture, matched by age, gravidity, and gestational age.

The frequency of occurrence of diabetes, hypertension, anemia, and premature birth were recorded for each group in accordance with standard criteria [5-7].

Final data were collected and statistically analyzed using the chi-square test.

Results

Of 2642 midstream urine specimens collected from pregnant females, 419 (15.8%) exhibited significant bacterial growth. One hundred eighty-eight (7.1%) subjects were asymptomatic and 231 (8.7%) had symptoms suggestive of UTIs.

Gram-negative micro-organisms were isolated in 89% of the specimens, and *Escherichia coli* was the most common, followed by *Klebsiella*.

Table 1 compares the age and gravidity of the symptomatic and asymptomatic groups with those in the control group. No statistically significant difference was found among these groups.

Development of hypertension and anemia during pregnancy was found to be more common in patients with significant bacteriuria in both the symptomatic and asymptomatic groups, compared with the control group ($P < 0.05$). The frequency of prematurity was statistically significant in symptomatic patients only, as compared with the control and asymptomatic groups ($P < 0.05$); however, no statistically significant difference was found between the control and asymptomatic groups. Tables 2 and 3 outline the occurrence of premature birth, diabetes, hypertension, and anemia in the control, asymptomatic, and symptomatic groups.

Discussion

Information regarding UTIs and their influence on pregnancy still remains incomplete for the Saudi population. Different reports published from various centers in the Kingdom have focused on the overall prevalence of UTIs. A preliminary report from Riyadh Military Hospital reported a

7.2% incidence of bacteriuria among 1886 urinary specimens obtained from male and female patients [8]. A second report from King Fahd Hospital of the University in Al-Khobar and King Faisal University in Dammam described the presence of significant bacteriuria in 17.4% of 530 inpatients and 5.7% of 1016 outpatients [9]. A third report from King Abdulaziz University Hospital, Jeddah, cited a 12.2% overall prevalence of UTI, and infection was more frequent in females than in males, with a ratio of 2:1 [10].

In our present study, we found 15.8% of the pregnant women had significant bacteriuria; 7.1% of them were asymptomatic and 8.7% were symptomatic. The 7.1% incidence of significant asymptomatic bacteriuria is comparable to that reported in the medical literature, with figures that vary from 2 to 10%, depending on the method used for testing and the socioeconomic status of the patients [11].

Despite earlier studies that showed the incidence of premature birth is higher in patients with bacteriuria [11], we found this to be true only for the symptomatic group. Patients in the asymptomatic bacteriuric group did not exhibit any significant difference from the control group in this regard.

Although diabetes is a multifactorial disease, its etiological relationship with significant bacteriuria during pregnancy remains unclear [11]. The fact that diabetes developed during pregnancy in a significant number of patients with bacteriuria, as compared with the control group in our study, is rather interesting. Whether this represents a possible result or a cause in this group of patients remains debatable.

Preeclampsia has been reported to occur more frequently when bacteriuria is present, although this finding has not been demonstrated universally [12].

Our study showed that hypertension and anemia in pregnancy are more common in women with bacteriuria, regardless of whether they have symptoms of UTI.

Our study did not consider the effect of treatment on the outcome of pregnancy and the various medical conditions associated with significant bacteriuria, but highlights the fact that the presence of significant bacteriuria during pregnancy puts the patient in a high-risk category, regardless of whether the patient is symptomatic or not.

References

1. Neu HC. Urinary tract infection in the 1980s. *Semin Urol* 1983;1:130-7.
2. Leight DA, Williams JD. Method for the detection of significant bacteriuria in large groups of patients. *J Clin Pathol* 1964;17:498-503.
3. Cowan ST. Cowan and Steel's manual for the identification of medical bacteria, ed 2. Cambridge: Cambridge University Press, 1981;103-15.
4. Wyngaarden JB, Lloyd H, Smith SC. Urinary tract infections and pyelonephritis. In: Cecil's textbook of Medicine, ed 17. Philadelphia: Saunders, 1985;619-23.
5. National Diabetic Data Group. Classification of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979;28:1039-47.
6. O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes* 1964;13:278-83.
7. McDonald-Gant R. Williams' obstetrics, ed 18. Norwalk, Connecticut: Appleton, Century, Crofts, 1989;chapter 28.
8. Severn M. Microbiology at Riyadh Military Hospital. *Saudi Med J* 1979;1:11-17.
9. Al-Sibai MH, Khwaja S, Al-Faraidy A, et al. Prevalence of bacteriuria in Saudi female patients. *Saudi Med J* 1982;8:376-81.
10. El-Tahawy AT, Khalaf RM. Urinary tract infection at a university hospital in Saudi Arabia: influence, microbiology, and antimicrobial susceptibility. *Ann Saudi Med* 1988;8:261-6.
11. Marchant DJ. Urinary tract infection in pregnancy. *Clin Obstet Gynecol* 1978;21:921-9.
12. Hill JA, Devoe LD, Bryands CL. Frequency of asymptomatic bacteriuria in pre-eclampsia. *Obstet Gynecol* 1986;67:529-32.

Special Communications

EVALUATION OF STUDENTS' PERFORMANCE AND EXAMINATION PROCEDURES IN FINAL CERTIFYING EXAMINATIONS IN INTERNAL MEDICINE (1982-1988)

Ezzeldin M. Ibrahim, FRCPI; Hassan Y. Al-Idrissi, Fachartz;
Hussain M. Al-Freihi, MD; Yussuf M. Al-Gindan, Fachartz

أجرينا تحليلاً ارتجاعياً لتقويم أداء ٤٥٩ طالباً في امتحاناتهم النهائية في تخصص الطب الباطني. جرت هذه الامتحانات خلال الفترة الممتدة من ١٩٨٢ - ١٩٨٨، وبلغت نسبة الرسوب فيها ١٧,٦٪. حصل مئتان وخمسة طلاب (٦,٤٤٪) على درجة "D" (٦٠ - ٦٩٪ من مجموع العلامات)، وحصل مائة وتسعة وثلاثون (١,٣٠٪) على درجة "C" (٧٠ - ٧٩٪ من مجموع العلامات)، فيما لم يحصل سوى ٧,٧٪ من الطلاب على نسبة أعلى من العلامات (٨٠٪ أو أكثر). لوحظ اتجاه عابر في امتحانات (١٩٨٨ - ١٩٨٦) الأخيرة تمثل في حصول نسبة أعلى على علامات أقل، ونسبة أقل على علامات أعلى، بالمقارنة مع امتحانات (١٩٨٢ - ١٩٨٤) التي سبقتها. كان أداء الطالبات عمومًا متوازيًا مع أداء الطلبة، وإن كان أداءهم أفضل من أدائهن بالنسبة للأسئلة ذات الخيارات المتعددة في الإجابة. كما أظهر التحليل انخفاضاً في معدل الإحراز بالنسبة للمقالات والامتحانات الشفهية والسريية في امتحانات (١٩٨٨ - ١٩٨٦) الأخيرة عما كان عليه في امتحانات ١٩٨٢ - ١٩٨٤ التي سبقتها. ولدى دراسة العلاقة المتبادلة بين عناصر الامتحان المختلفة تبين أن الأسئلة ذات الخيارات المتعددة في الإجابة كانت الأكثر ترابطاً مع الإجراءات الأخرى. ولوحظ ترابط أقل بالنسبة للامتحان السريري. وأظهر تحليل العوامل أيضاً أن تحميل العوامل كان الأعلى بالنسبة للأسئلة المشتملة على أجوبة متعددة الخيارات، والأدنى بالنسبة للامتحانات السريية. كما لوحظ انخفاض الترابط وتحميل العوامل بالنسبة للجزء الخاص بالمقالات. وبينما يلاحظ كيف تم حذف ورقة المقالة بحكمة من المنهج الحديث، فإن بياناتنا تقترح ضرورة استبدال الامتحان السريري التقليدي بطريقة منهجية تعتمد تركيباً بنوياً أكثر موضوعية. إن تحليلنا قد يصلح كدليل لصياغة الامتحانات النهائية في جميع كليات الطب بالملكة.

We conducted a retrospective analysis to evaluate the performance of 459 students on their final certifying examination in internal medicine. These examinations were taken during 1982 through 1988, and the failure rate was 17.6%. Two hundred and five students (44.6%) received grade D (60-69% of total marks) and 139 (30.1%) grade C (70-79% of total marks). Only 7.7% of the students scored higher (80% or more). A temporal trend has been observed in that a higher percentage of lower grades and lower percentage of higher grades has been

From the Department of Internal Medicine, College of Medicine and Medical Sciences, King Faisal University, Dammam.

Address reprint requests and correspondence to Dr. Ibrahim: King Fahd Hospital of the University, P.O. Box 40004, Al-Khobar 31952, Saudi Arabia.

Accepted for publication 4 June 1990.

observed in recent (1986–1988), compared with earlier (1982–1984) years. Female students generally performed on a par with males, though male students performed better on multiple choice questions (MCQs). The analysis also showed lower mean scores for the essay, oral, and clinical components in recent (1986–1988) than in earlier (1982–1984) years. In studying the interrelationship between different examination components, the MCQs were found to have the highest correlation with other procedures. A lower correlation was observed for clinical examination. Factor analysis also showed that MCQs had the highest and clinical examinations the lowest factor loading. Low correlation and factor loading were also noted for the essay portion. While in the newly implemented curriculum the essay paper has been wisely eliminated, our data suggest that the traditional clinical examination should be replaced by a more objective and structural method. Our analysis may serve as a guide for formulation of final certifying examinations in medical schools throughout the Kingdom.

The rapid founding and growth of medical schools in Saudi Arabia has elicited valuable views and recommendations concerning how to achieve the highest standards in undergraduate curricula and postgraduate training programs [1–5]. One important means of attaining these standards is to assess the product of a given system [6]. Equally important is to appraise the reliability, validity, and practicality of the various methods used to evaluate the skill and knowledge of undergraduate and postgraduate medical students [7–9]. The current analysis was undertaken to assess these tools.

Material and Methods

Between 1982 and 1988, ten final certifying examinations in internal medicine were conducted, based on the old curriculum, and these were administered at the College of Medicine and Medical Sciences of King Faisal University [2]. In the old curriculum, final certifying examinations in internal medicine were composed of the following: (1) MCQs which represented 30% of the total marks; (2) an essay which consisted of 10% of the grade; (3) a clinical examination, which represented 50% of the total marks and consisted of one long case and two or more short cases; and (4) a viva examination, which made up 10% of the total marks.

An overall grade of 60% or more was considered passing, regardless of the scores for the individual components. The grading scheme was as follows: grade A, 90% or more; grade B, 89 to 80%; grade C, 79 to 70%; grade D, 69 to 60%; and grade F, below 60%.

Data Analysis and Statistical Methods

Comparison of proportions of failed versus

passed students according to sex and year of examination was performed using *chi-square* analysis [10]. Comparison of male versus female students' mean total score and mean scores of various examination components was carried out using analysis of variance [11]. Because of an apparent difference between the students' performance in different years, a post hoc comparison of the mean scores in different years was done using Scheffe's methods [11]. Correlation between different examination components was estimated using Pearson's product-moment method [10]. Factor analysis was also carried out to study the intercorrelations of various examination components by clustering them into factor(s) or a summary score [12]. The varimax method was used for orthogonal factor rotation [13]. In all analyses, a two-sided *P* value of less than 0.05 was considered significant. The BMDP Statistical Software programs (PID, P6D, P4F, and P4M) were used to analyze the data [14].

Results

The first certifying examinations in internal medicine involved 459 examinees, and this includes students who failed one or more times. We determined that the results and conclusions of the analyses would not be significantly skewed by including the test results of those students who failed and retook the examination.

Table 1 shows the distribution of students' grades broken down by sex and year of examination. About three-quarters of all students had grade D (205 students, 44.6%) or C (138 students, 30.1%); only 6.98% (*N* = 31) and 0.9% (*N* = 4) of the students achieved grade B or A, respectively. The overall failure rate was 17.6% (*N* = 81). There was no significant correlation between the

TABLE 1. Distribution of students' grades according to sex and examination years.

	Grades No. (%) ^a					Total(%) ^b
	F	D	C	B	A	
Sex						
Males	46(18)	117(46)	72(28)	19(7)	3(1)	257(56)
Females	35(17)	88(43.5)	66(33)	12(6)	1(0.5)	202(44)
Year						
1982	8(18)	11(24)	14(31)	9(20)	3(7)	45(9.8)
1983	8(16)	19(37)	18(35)	5(10)	1(2)	51(11.1)
1984	9(19)	17(35)	16(33)	6(13)	0(0)	48(10.5)
1985	6(12)	20(40)	21(42)	3(6)	0(0)	50(10.9)
1986	17(20)	42(50)	22(26)	3(4)	0(0)	84(18.3)
1987	24(21)	57(50)	30(26)	3(3)	0(0)	114(24.8)
1988	9(14)	39(58)	17(25)	2(3)	0(0)	67(14.6)
Total	81(17.6)	205(44.6)	138(30.1)	31(6.8)	4(0.9)	459

^aRow percentage.^bColumn percentage.

TABLE 2. Mean total scores of student's performance in different examination components and according to sex and examination year.

Group (No.)	Score (mean $\pm$ SD) ^a			
	MCQ(30%)	Essay(10%)	Clinical(50%)	Oral(10%)
All students (N = 459)	19.34 $\pm$ 2.95	6.55 $\pm$ 1.16	33.43 $\pm$ 4.75	6.73 $\pm$ 1.26
Sex				
Males (N = 257)	19.69 $\pm$ 2.82*	6.47 $\pm$ 1.69	33.08 $\pm$ 4.71	6.66 $\pm$ 1.40
Females (N = 202)	18.94 $\pm$ 3.05	6.66 $\pm$ 1.42	33.88 $\pm$ 4.79	6.81 $\pm$ 1.04
Year of examination				
1982 (N = 45)	18.75 $\pm$ 3.55	6.89 $\pm$ 1.24	35.90 $\pm$ 6.52**	7.93 $\pm$ 1.29**
1983 (N = 51)	18.58 $\pm$ 2.51	6.72 $\pm$ 1.01	35.53 $\pm$ 5.62**	6.80 $\pm$ 1.23
1984 (N = 48)	19.72 $\pm$ 3.04	7.24 $\pm$ 1.43**	33.52 $\pm$ 4.80	6.61 $\pm$ 1.36
1985 (N = 50)	20.39 $\pm$ 2.62	6.35 $\pm$ 1.38	33.53 $\pm$ 4.54	6.69 $\pm$ 1.80
1986 (N = 84)	19.18 $\pm$ 2.94	6.18 $\pm$ 1.06	32.28 $\pm$ 4.44	6.58 $\pm$ 1.31
1987 (N = 114)	19.29 $\pm$ 2.89	6.72 $\pm$ 0.81	32.28 $\pm$ 4.11	6.54 $\pm$ 1.07
1988 (N = 67)	19.71 $\pm$ 2.88	6.06 $\pm$ 1.08	32.95 $\pm$ 2.88	6.46 $\pm$ 1.03

^aPercentage in parentheses represents the portion of the total score. * $P = 0.0059$ (analysis of variance). ** $P < 0.001$ (Scheffe's multiple-comparison method) in essay between 1984 versus 1986 or 1988; in the clinical portion between 1982 or 1983 versus 1987; in the oral portion between 1982 versus 1983–1988. MCQ = multiple-choice questions.

distribution of various grades and student sex ($P = 0.8$). However, there was a trend toward a higher percentage of F and D grades and lower percentage of B or A grades in recent years (1986–1988) compared with those in earlier years (1982–1984). This trend was highly significant at $P < 0.0001$.

The relationship between passing the clinical examination (60% of the allocated 50 marks) and passing the overall final examination was also assessed. Thirty-six of 102 students (35.3%)

scored 60% or better on the total final score despite failing the clinical component.

The results of the analysis of students' scores in different sections of the final certifying examination are shown in Table 2. Males had significantly higher scores on the MCQ than did females (F value = 7.66, $DF = 1, 457$, $P = 0.0059$); however, no other significant differences were noted for the other examination components. There was also a significant trend toward higher scores on the essay, clinical or oral, in earlier years compared

TABLE 3. *The correlation between students' scores in different examination components.*

A. Correlation matrix (correlation coefficients) of students' scores in individual examination components				
	MCQ	Essay	Clinical	Oral
MCQ	1.00	0.441*	0.405*	0.429*
Essay		1.00	0.369*	0.368*
Clinical			1.00	0.397*

B. Correlation between students' scores of each examination component and the combined scores of the other three				
MCQ	vs	essay + clinical + oral	0.500*	
Essay	vs	MCQ + clinical + oral	0.487*	
Clinical	vs	MCQ + essay ± oral	0.488*	
Oral	vs	MCQ ± clinical ± essay	0.501*	

* $P < 0.001$ (correlation coefficient).

with those for more recent years.

The correlation matrix of various examination components is shown in Table 3 where the highest correlations were linked to MCQs. Also examined was the correlation between scores in each examination component and the combined scores of all other parts (Table 3). Again, a low—though significant—correlation was estimated for essay or clinical components as compared to MCQs or oral examinations. Evaluating the correlation between examination components in each grade (i.e., F, D, C, and AB [grades A and B combined]) was also attempted. Lower levels of correlation were found between components for each grade (data not shown). Also shown was the negative, though insignificant, correlation between MCQs and the clinical assessment for students with grades F, D, and C (data not shown).

The interrelationship between examination components was also tested using factor analysis. Only one factor derived had an eigenvalue greater than unity (2.206), and accounted for 55% of the variance in the total students' score. The model showed that rotated factor loadings were 0.774, 0.738, 0.731, and 0.727 for MCQs, oral, essay, and clinical components, respectively. The data indicate that, while the MCQ score has the highest loading, the clinical score accounted for the lowest value.

Discussion

Assessment of various evaluation procedures is as important a task as teaching students [7–9,15].

Analysis of the overall students' performance has clearly shown that grades were not uniformly distributed into a normal curve. While there was an acceptable failure rate of 17.6%, a considerable proportion of students scored C (44.7%) or D (30.1%). Conversely, only a small proportion of students achieved grade B (6.8%) or A (0.9%). Students sex did not account for the grade distribution. The similarity in performance between male and female students agrees with our previously reported observation [6]. The year of examination was a significant variable and may explain the observed skewed pattern whereby there was a higher percentage of F and D grades and lower prevalence of B and A grades in recent years (1986–1988) compared with those in earlier years (1982–1984). The difference in student performance between earlier and recent years cannot be attributed to students' repeating examinations they had failed, as conclusions were not altered by analyzing only the first performance of each student. Also the inclusion of repeated observations for those who failed before cannot explain the low prevalence of B or A grades in recent years. It is conceivable that less qualified students were accepted into medical school in more recent years. However, variability in examiners and reliability of examination procedures may be the main explanations for this temporal trend.

Studying the correlation between the various individual examination components demonstrated an acceptable degree of concordance between them. The analysis, however, showed that MCQs prevailed as the component that correlated highest with all the others. Factor

analysis also showed that MCQs had the highest loading value. Our data, therefore, bore out the known objectivity of that tool [8,16], and reconfirm a previously reported analysis from our facility [7]. However, to enhance or at least maintain that high discriminating function, MCQ examinations should be regularly subjected to psychometric analyses [17] and reliability and validity testing [18].

Oral examination was also shown to possess a reasonably high degree of correlation with other components separately or combined. Particularly high was the correlation between MCQs and the oral examination. A similar good correlation between the two components has been reported previously [15].

Although the problem-oriented essay examination was significantly correlated with other examination components, the correlation was relatively low. This poor reliability and validity of essay questions caused the National Board of Medical Examiners of the United States to convert this portion of the evaluation to MCQs [18].

In our experience the traditional clinical examination had the least correlation with all other evaluation components. It was also disturbing to note that 35.3% of those who failed the clinical examination were able to achieve an overall passing score. Conventional clinical evaluation is often subjective and lacks validity and reliability [8,15,19,20], thus a design for an objective structured clinical examination was first introduced by Harden and Gleeson [19] to assess various aspects of clinical skills. The reliability and validity (content, criterion, and construct validity) of the proposed design, as compared to the more traditional procedures, was proved in several studies [9,15,21].

Certain modifications have been made in the newly implemented curriculum to influence the weight and the design of the final certifying examination [2]. The final examination in internal medicine is now composed of MCQs, a viva, and a traditional clinical examination, accounting for 35%, 15%, and 50% of the total marks, respectively. It is also now mandatory for students to pass the clinical component with a minimum of 60%.

Our data should serve as a basis for future assessment of the new curriculum. The perfor-

mance of our students should also be compared with that from other medical schools within the Kingdom. The derived data should help influence the format of the final certifying examination in internal medicine. Thus, for the same reason that the poorly reliable essay paper was eliminated from the written examination in the new curriculum, it may also be appropriate for the traditional clinical procedure to be replaced by a more objective and structured clinical test. This test may be combined with an oral component. Data about this modification would be very useful for future analysis.

References

1. Cudkovic L. A medical school without walls. In: Proceedings of the 4th Saudi medical conference. 1980;333-41.
2. Al-Sibai HM, Al-Freih HM, Lutfi AM, et al. Evolution of the undergraduate curriculum at the College of Medicine, King Faisal University. *Ann Saudi Med* 1989;9(1):64-71.
3. Al-Nozha MM. Postgraduate medical education in Saudi Arabia: the present and the coming decade. *Ann Saudi Med* 1985;5(4):197-8.
4. Herdson PB. The organization of postgraduate medical training in the Kingdom of Saudi Arabia. *Ann Saudi Med* 1987;7(1):1-2.
5. Al-Nozha MM, Taher S. Saudi Arabian postgraduate medical board: will the dream come true? *Ann Saudi Med* 1987;7(3):175-6.
6. Ibrahim EM, Al-Freih HM, Rihan TT, Al-Sohaibani MO. Comparative study of students' performance at pre-medical, preclinical, and clinical levels. *Ann Saudi Med* 1988;8(6):481-4.
7. Luqman W, Ibrahim E. The outcome for some methods of evaluation of clinical students. *Mater Med Pol* 1987;19:60-1.
8. Hubbard JP. Measuring medical examinations: the tests and the experience of the National Board of Medical Examiners, ed 2. Philadelphia: Lea & Febiger, 1978.
9. Robb KV, Rothman AI. The assessment of history-taking and physical examination skills, in general internal medicine residents, using check-list. *Ann R Coll Phys Surg Can* 1987;20(1):45-7.
10. Daniel WW. Biostatistics: a foundation for analysis in the health science, ed 4. New York: Wiley, 1987.
11. Godfrey K. Comparing the means of several groups. In: Bailer JG, Mosteller F, eds. *Medical uses of statistics*. Boston: New England Journal of Medicine Books, 1986;205-34.
12. Frane JW, Hill M. Factor analysis as a tool for data analysis. *Commun Statist Theor Meth* 1976(A5):487-506.
13. Kaiser HF. The varimax criterion for analytic rotation in factor analysis. *Psychology* 1958;23:187-200.
14. Dixon WJ, Brown MB, Engelman L, et al. *BMDP Statistical Software Manual*. Berkeley: University of California Press, 1988.
15. Ginsburg AD. Comparison of intraining evaluation with

- tests of clinical ability in medical students. *J Med Educ* 1985;60:29-36.
16. Hubbard JP, Clemans WV. Multiple-choice examination in medicine. Philadelphia: Lea & Febiger, 1961.
 17. Schumacher CF. Scoring and analysis. In: Hubbard PJ, ed. Measuring medical education: the tests and the experience of the National Board of Medical Examiners, ed 2. Philadelphia: Lea & Febiger, 1978;48-58.
 18. Schumacher CF. Reliability, validity and standard setting. In: Hubbard JP, ed. Measuring medical education: the tests and the experience of the National Board of Medical Examiners, ed 2. Philadelphia: Lea & Febiger, 1978;59-71.
 19. Harden RM, Gleeson FA. Assessment of clinical competence using an objective structured clinical examination. *Med Educ* 1979;13:41-54.
 20. Marienfeld RD, Reid JC. Subjective vs objective evaluation of clinical clerks. *N Engl J Med* 1980;302(18):1036-7.
 21. Robb KV, Rothman AL. The assessment of clinical skills in general medical residents: comparison of the objective structured clinical examination to a conventional oral examination. *Ann R Coll Phys Surg Can* 1985;18(3):235-8.

AN APPRAISAL OF THE UTILIZATION OF ANTENATAL SERVICES IN PRIMARY HEALTH CARE

Abdulaziz Nasser Al-Nasser, MRCGP

أجريت هذه الدراسة لتقويم ممارسة المستفيدات من خدمات الحوامل المقدمة في مراكز الرعاية الصحية الأولية، ومدى ترابط النتائج مع بعض عوامل الخطر ومآل الحمل. قمنا بدراسة السجلات الطبية لـ ١٩٤٦ من النساء الحوامل اللواتي يتلقين عناية ما قبل الولادة في مراكز الرعاية الصحية الأولية في منطقة الباحة. تبين أن معظم النساء (٥٨,٥٪) راجعن العيادة خمس مرات أو أقل، فيما راجع ١٥,٢٪ منهن فقط أكثر من ثماني مرات. لم يكن هناك ترابط واضح بين سن الأم وتواتر الزيارات. بينما كان هناك ترابط إحصائي مهم بين عدد زيارات الحمل قبل الولادة من جهة وبين عدد مرات الإنجاب وعمر الحمل لدى أول زيارة ومكان الولادة ومآل الحمل من الجهة الأخرى ($P > 0.05$) شوهدت أغلبية الحوامل (٦٠,٨٪) أول مرة قبل الأسبوع العشرين من الحمل. و٨٪ من الحوامل في المراكز الصحية و١٦,٤٪ في البيوت. ولوحظ ترابط واضح بين عمر الأمومة وعدد مرات الإنجاب وعمر الحمل عند المراجعة. كما لوحظ وجود ترابط مع قصة سابقة للإجهاض المتكرر وموت الجنين داخل الرحم. ولم تظهر علاقة بين عمر الأمومة لدى المراجعة الأولى وبين حدوث نزف سابق أو عمليات قيصرية.

This study was done to evaluate the practice of users of the antenatal care services of the primary health care centers, and correlates our findings with some of the risk factors and the outcome of the pregnancies. The records of 1946 women receiving antenatal care in the primary health care centers in Al-Baha region were reviewed. The majority of the women (58.5%) visited the clinic five times or less, while only 15.2% visited more than eight times. There was no significant association between maternal age and the frequency of visits. There was a statistically significant association between parity, gestational age at first visit, place of delivery, and outcome of the pregnancy on one hand and the number of antenatal visits on the other ($P < 0.05$). The majority of pregnant women (60.8%) were first seen before the 20th week of gestation. Eight percent delivered in the centers and 16.4% delivered at home. There were significant associations between maternal age, parity, and gestational age at presentation. There was also an association with a previous history of recurrent abortions and intra-uterine fetal death. Previous bleeding and cesarean sections showed no significant relationship with maternal age at the time of first presentation.

Maternal and child health care is a major component of the primary health care approach for achieving health for all by the turn of the century. Recently, there has been very rapid improvement

in the provision of health care services in Saudi Arabia, and following the Alma Ata declaration in 1978, primary health care centers were established and these are widely and uniformly distributed throughout the country. Since the 1930s, routine antenatal care requires monthly attendance at the clinics up to 28 weeks of gestation, followed by fortnightly attendance up to 36 weeks, and thereafter weekly attendance to term. This approach has yet to be revamped [1-3]. The antenatal care program of the primary health care

From the Department of Family and Community Medicine, College of Medicine, King Saud University, Riyadh.

Address reprint requests and correspondence to: Dr. Al-Nasser: Department of Family & Community Medicine (34), College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Accepted for publication 18 June 1990.

system in Saudi Arabia has adopted this approach.

The present study was designed to assess the utilization pattern of the antenatal care services of the primary health care centers in Saudi Arabia and correlates this with some of the demographic and risk factors. The findings in this study may influence the future pattern of the provision of such services in the primary care setting.

Material and Methods

A retrospective study was conducted in which the records of all women who received antenatal care services in all primary health centers of the Al-Baha region of Saudi Arabia between the beginning of 1987 and the end of 1988 were examined.

There are 75 centers, four general hospitals, and one maternity hospital distributed throughout the region. Most of the risk factors or causes of perinatal mortality or morbidity could not be tested, because the policy in the centers is to refer clearly high-risk patients to the hospital. The data extracted from the antenatal records included age of mother, parity, gestational age at first visit to clinic, number of visits, laboratory investigations, antenatal services provided, place of delivery, and outcome of pregnancy.

The data collected were processed by micro-computer using the Systat software to provide frequency distribution and other bivariate analysis. The significance of the relationship between any two categorical variables was examined by the chi-square test at a probability level of 5%.

Results

A total of 1946 records of women attending the antenatal clinic of the primary health care centers during the period of study were examined. The nationality of 11 patients (0.5%) of the sample was unknown; a sizable proportion ($N = 1684$; 86.5%) were Saudis while 12.9% ($N = 251$) were non-Saudis. The age distribution is almost the same for both the Saudi and non-Saudi population, with about 84% between the ages of 18 and 35 years. There is a significant nationality differential in the parity distribution ($P < 0.001$); the non-Saudis have a higher proportion of low-parity

women than do the Saudis. Also, 14.7% of the study sample presented for the first time at the clinic after 28 weeks of gestation, with the non-Saudis presenting earlier at the clinics than did their Saudi counterparts. A higher significant proportion of the non-Saudis deliver at the hospitals ($P < 0.001$), whereas home deliveries are more common among the Saudis.

The frequency of antenatal visits was examined in relation to some fertility variables, and the findings are shown in Table 1. A majority of the women (58.5%) visited the clinic less than six times, while only 15.2% visited more than eight times. There was no significant association between the age of the mother and frequency of visits at the antenatal clinics ($P > 0.1$). However, there are statistically significant associations between parity, gestational age at first visit, place of delivery, and outcome of pregnancy on one hand and the number of antenatal visits on the other ($P < 0.05$).

The proportion of women who visited the clinic more than eight times declined progressively with increasing parity. Also, those who presented early at less than 20 weeks' gestation had a higher number of visits than did women who presented after 20 weeks. Those women delivering either at the center or in the hospital represented 64.7% of the sample, while 16.4% of the deliveries took place at home. The place of delivery could not be traced in 368 (18.9%) of the study sample.

A higher proportion of those who delivered at either the center or hospital visited the clinics more than five times, and women with normal deliveries had fewer antenatal visits than did those who were delivered by cesarean section. Nearly 40% of those whose mode of delivery was unknown visited the clinic less than three times. The analysis of the association between previous recurrent abortions, cesarean section, intra-uterine fetal death, and anemia on one hand and the frequency of antenatal visits on the other did not show any statistical significance ($P > 0.1$).

The distribution of women by gestational age at first presentation for antenatal care was analyzed in relation to some maternal variables and obstetric problems. Less than 20% of the study sample presented at less than 10 weeks' gestation, while 14.7% presented after 28 weeks. A majority (60.8%) presented by 20 weeks' gestation. There

TABLE 1. The percentage frequency distribution of antenatal visits by age, parity, time of presentation, pregnancy outcome, and previous obstetric problem.

Variables	Sample size	<3	3-5	6-8	8+
Age					
< 18	63	17.5	33.3	27.0	19.0
18-25	750	28.4	31.5	20.8	15.6
26-35	892	24.0	33.9	23.4	15.6
35+	237	21.9	37.6	24.9	11.4
Unknown	4				
Parity^a					
Prima	250	24.8	29.2	21.6	22.4
1-5	943	27.2	32.6	22.1	14.1
6-8	461	21.5	36.9	24.3	15.1
> 8	263	24.7	34.6	23.6	12.5
Unknown	29	24.1	27.6	17.2	13.8
Gestational age at 1st presentation (wk)					
< 10	394	18.5	20.3	24.6	34.0
10-20	791	14.8	35.1	30.5	17.6
21-28	413	32.0	45.0	19.6	3.4
> 28	286	57.7	32.9	5.9	1.4
Unknown	62	22.6	17.7	9.7	6.4
Place of delivery					
In the center	155	12.3	29.0	25.2	29.0
At home	320	24.4	35.9	25.9	11.6
In hospital	1103	22.8	34.1	22.2	17.1
Unknown	368	38.3	30.7	20.4	6.5
Mode of delivery (outcome^b)					
NSVD	1487	21.9	34.0	23.5	17.2
Instrumental	8	0.0	25.0	25.0	37.5
CS	74	16.2	29.7	24.3	21.6
Abortion	26	57.6	30.8	11.5	0.0
IUFD	10	30.0	20.0	20.0	10
Recurrent abortion					
Yes	90	16.7	33.3	27.8	15.6
No	1856	25.6	33.3	22.5	15.1
Previous CS					
Yes	57	19.3	35.1	19.3	19.3
No	1889	25.4	33.3	22.8	15.0
Previous IUFD					
Yes	33	21.2	33.3	27.3	12.1
No	1913	25.2	33.3	22.6	15.2
Total	1946	490	649	442	295

^aSignificant at 5% probability level.^bSignificant at 1% probability level.

Note: non-respondents have been excluded from the statistical analysis.

NSVD = normal spontaneous vaginal delivery; IUFD = intrauterine fetal death; CS = cesarean section.

are significant associations between maternal age, parity, and gestational age at presentation ($P < 0.001$). A higher proportion of the older women presented after 20 weeks of gestation, while women with low parity presented earlier. There was no relationship between the place of delivery and the gestational age at first visit to the clinic ($P > 0.2$). However, a significantly higher proportion of women whose pregnancy ended either in

abortion or in intrauterine fetal death presented at a gestational age of less than 10 weeks ($P < 0.01$). There was also a statistically significant association between the gestational age at presentation ($P < 0.05$) and a previous history of recurrent abortions and intrauterine fetal deaths. Previous bleeding and cesarean sections had no significant relationships with the age at first presentation for antenatal care.

Discussion

In this study, the majority of women at all ages visited the centers for antenatal care five times or less. This could be attributed to many reasons, including the relatively new introduction of this service in the rural community after full implementation of the primary health care program and the shift of antenatal care follow-up from the center to hospital maternity unit or to another center, sometimes without notice. Other factors may include a change in residency for some of the women, especially at the end of pregnancy, so that delivery can take place at the family home. In addition, some women may not be convinced of the benefits of attending frequently for what they consider a physiological phenomenon. This latter point may explain the progressive decline in the frequency of visits among high-parity women [4].

The higher percentage of non-Saudi women with lower parity presenting earlier for antenatal care and subsequently delivering at hospital units can be explained by their higher level of education. The non-Saudis are expatriates who either come to teach in schools or to accompany their husbands who are involved in skilled or professional work.

Delivery at home, which is virtually no longer practiced in the cities, is still practiced in rural communities, as 320 women (16.4%) delivered at home [5]. The reason for this could be the fact that the primary care centers have recently been upgraded and not all may have delivery facilities. Hence the practice of classifying the pregnancies as high risk or low risk. While encouraging low-risk mothers to obtain all antenatal care from the center and to deliver at the center or at home, supervised by a midwife if requested, high-risk mothers are referred to hospital units, especially in the later stages of pregnancy, though antenatal care may be provided by the centers. This distinction between low- and high-risk pregnancies would have been more accurate if different schemes of visits were stipulated for the low- and high-risk mothers. This is also evidenced by the finding that no significant association was found between either a poor obstetric history (recurrent abortion, previous cesarean section, or previous intrauterine fetal death), or medical problem (anemia) on one hand, and the frequency of

antenatal visits on the other. These conditions are indicative of high-risk pregnancies, and affected mothers would have been compelled to have more regular visits [6-9].

Although early presentation for antenatal care is encouraged and the majority of women presented before 20 weeks, 14.7% of the women presented after the 28th week of gestation. The high-parity women also supported the need for a modified scheme and an improvement in the health education talk given during antenatal visits.

It may be premature to recommend an optimum number of visits for antenatal care service based on the results of this study. However, the study showed that 85% of the women visited eight times or less. This is in agreement with the views of some obstetricians and general practitioners who had advocated between six and eight antenatal visits for low-risk pregnancies and a higher number for high risk [2,3,9]. Further studies may be necessary to arrive at a more accurate picture [7,8].

Notwithstanding, it may now become necessary to review the antenatal care service in primary care facilities and hospitals regarding not only the number of visits but the content of each visit, the person in charge of each visit (i.e., the doctor, the nurse, or midwife), and even the system of providing this service through special antenatal clinics or among regular patient flow. To achieve an optimum antenatal care, there are important factors that have to be taken into consideration, including the actual use of this service and patient compliance with the existing scheme, the classification of pregnancies as low or high risk, the opinion and experience of the provider of this service, and the opinion of the women concerned.

Acknowledgment

I would like to extend my thanks and appreciation to the Primary Care Programme Coordinators in Al-Baha region and to all primary health care staff for their help and cooperation.

References

1. Heringa MP, Huisjes HJ. Antenatal care, current practice in debate. *Br J Obstet Gynaecol* 1988;95(9):836-40.
2. Marsh GN. New programme of antenatal care in general practice. *Br Med J* 1985;291:646-8.
3. Hall MH, Ching PK, MacGillivray I. Is routine antenatal care worthwhile. *Lancet* 1980;2:78-80.
4. Enkin M, Chalmer L. Effectiveness and satisfaction in

- antenatal care. London: Heinemann, 1982.
5. Marsh GN, Cashman HA, Russel IT. General practitioner obstetrics in northern region in 1983. *Br Med J* 1985;290:901-3.
 6. Young G. Are isolated maternity units run by general practitioners dangerous? *Br Med J* 1987;294:744-6.
 7. Hakansson A. Comparison between the outcome of antenatal care led primarily by district physician or by obstetrician: a study on a defined population based on the medical birth registry. *Acta Obstet Gynecol Scand* 1988;67(7):639-44.
 8. Thomas H, Draper J, Field S, Hare MJ. Evaluation of an integrated community antenatal clinic. *J Coll Gen Pract* 1987;37(305):544-7.
 9. Draper J, Field S, Thomes H, Have MJ. Antenatal visits: a comparative study between integrated and shared antenatal care. *J Obstet Gynaecol* 1986;7:1-6.

PUBLIC ATTITUDE AND ACCESSIBILITY CONCERNING KIDNEY DONATION CARD AND LIVING RELATED DONATION IN RIYADH, SAUDI ARABIA

Sulaiman Al-Shammari, MRCGP

أجرى استقصاء لدى أفراد عينة عشوائية، مكونة من ٧٥٣ شخصاً من السعوديين وغير السعوديين، لتبين مواقفهم من بطاقة التبرع بالكلية ومن تبرع قريب حي بكلية وذلك باستخدام استبيان. كان متوسط العمر للعينة ٣٠,٧ سنة (الانحراف المعياري ± 11) ونسبة الإناث ٣٦٪. كانت أكثرية العينة من السعوديين (٨٧٪) ونسبة المتزوجين ٥٤٪، شكّل الطلبة والمدرسون أكبر المجموعات المهنية في حين كانت نسبة الأميين ٨,١٪ فقط من العينة. لم نجد فرقاً مهماً بين السعوديين وغير السعوديين فيما يتعلق باستعدادهم للتوقيع على بطاقة التبرع بالكلية، ولم يكن قد وقع فعلاً على بطاقة التبرع سوى ١٨,٢٥٪ من جميع فئات الأعمار بالرغم من أن ما نسبته ٥٢,٧٪ من المجيبين أبدوا استعدادهم لتوقيعها. كانت نسبة من يعرفون البطاقة ومستعدين لتوقيعها أعلى بدرجة مهمة ($P < 0,05$) فيمن هم دون سن الثلاثين. كان الوعي أكثر والاستعداد أكبر لدى الذكور والمتزوجين. كما تزايد الوعي والاستعداد لتوقيع البطاقة ($P < 0,04$) مع ازدياد مستوى التعليم. ولم يكن هناك تأثير للسن أو الجنس أو الحالة العائلية أو الجنسية أو المهنة أو التعليم على الاستعداد للتبرع بالكلية أثناء الحياة. كان ٤٢٪ من إجمالي المجيبين مستعدين لتوقيع البطاقة كما كانوا مستعدين للتبرع أثناء الحياة في حين كان ١٠,٦٪ منهم فقط غير مستعدين لتوقيعها ولا للتبرع أثناء الحياة.

The attitudes of a random sample of 753 Saudis and non-Saudis toward the kidney donation card and living related donation were examined using a structured questionnaire. The mean age of the sample population was 30.7 years ($SD \pm 11$ years) and 36% were females. The majority were Saudis (87%) and 54% were married. Students and teachers represent the largest occupational groups and only 8.1% were illiterates. There was no significant difference between Saudis and non-Saudis regarding willingness to sign kidney donor cards. Only 18.25% of all age groups had already signed a kidney donor card, even though 52.7% of the respondents were willing to sign one. A significantly higher proportion ($P < 0.05$) of those below 30 years old were aware of kidney donor cards and were willing to sign one. The awareness and willingness were greater among male and married subjects. As the level of education increased, the degree of awareness and inclination to sign a kidney donor card also increased ($P < 0.04$). There was no differential effect of age, sex, marital status, nationality, occupation, and education on the willingness to donate kidneys during life. Of the total respondents, 42% were willing to sign a kidney donor card as well as to donate during life. Only 10.6% of the respondents were neither willing to sign a kidney donor card nor to donate during life.

From the Department of Family and Community Medicine and Primary Care Clinics at the University Hospitals, King Saud University.

Address reprint requests and correspondence to Dr. Al-Shammari: Department of Family and Community Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Accepted for publication 12 June 1990.

End-stage renal failure is a serious health problem in the Kingdom of Saudi Arabia, and the size of the problem is increasing gradually. There were 120 cases in 1983. According to a recent finding published in 1989, there were 1973 patients on chronic hemodialysis distributed over 61 centers in the Kingdom [1,2]. It is estimated that the inci-

dence of this disease is 100 per million per year in the Kingdom, which is higher than the incidence in Europe [3]. Renal transplant services are now well established in Saudi Arabia. However, more than 65% of the patients with end-stage renal failure remain on the waiting list for transplant therapy due to a shortage of donor organs.

In many Middle Eastern countries, including Saudi Arabia, the usual sources of organs for transplantation are living related organ donation or imported renal graft. Another alternative is sending the patients abroad for cadaveric renal transplant. These measures only partially solve the problem as it exists in the Kingdom. More appropriately, the Kingdom of Saudi Arabia has established a cadaveric renal transplant program and a national kidney foundation center. A campaign conducted through the various information media was mounted to inform the public of organ procurement [1,2]. Road traffic accidents claim more victims in Saudi Arabia than in Europe, and yet there is a greater shortage of donor organs in the Middle East than in Europe. These victims are usually young adults and can be a suitable source of cadaveric organ donation [3,4].

Organ transplantation has been the subject of much attention, but no study has been published about public attitudes toward organ donation in Saudi Arabia. This project was carried out with the following objectives in mind: (1) to assess attitudes and behavior in the local community toward kidney donation; and (2) to determine the availability of kidney donor cards to the general public.

Material and Methods

A stratified random sample of Riyadh residents 18 years and older was selected and the required information was collected. The selected sample represented both sexes and different socioeconomic, cultural, occupational, and educational groups.

The questionnaire was self-administered to literate respondents, while trained interviewers assisted the illiterate respondents in completing the questionnaire.

The predesigned information sheet contained a multiplicity of questions to determine certain

relevant items and concepts, such as age, sex, nationality, residence, educational level, occupation, marital status, and the attitude toward having a kidney donation card. The study was started in Shaaban 1409 (March 1989) and continued for 4 to 5 months in order to cover 800 interviewees. The data on the completed information sheets were analyzed using a microcomputer. The statistical software package (stat pack) was used to produce a frequency distribution of variables and other relevant cross tables.

Results

The data for statistical analysis in this study were obtained from 753 respondents, yielding a 94.1% response rate. The mean age of the respondents was 30.7 years ($SD \pm 11$ years), while the modal age was 23 years. Female respondents represented 36% and 87% were Saudi nationals. Marital status of the respondents was as follows: 54% were married, 42% were single, and only 4% were either widowed or divorced. The majority of the occupations in the Saudi community were represented, but students (29%), teachers (18%), military personnel (16%), and administrators (13.5%) were in the majority. Most respondents were educated, as 41.4% were either university students or graduates and a further 29.5% had reached secondary school. The illiterate represented only 8.1% of the sample (Table 1).

Table 1 also shows the respondents' attitudes toward the kidney donor card according to their demographic characteristics. The table shows there was a significant relationship between respondents' attitudes toward the donor card and age, sex, marital status, occupation, and education ($P < 0.01$ in each case). A higher proportion of those below 30 years were aware and willing to sign the donor card. Nine percent of the males were not aware of the donor card, compared with 19% of the females; 56% of the males were willing to sign a card compared with 47% of the females.

Although non-Saudis represented only 13% of the sample, it appears that the findings in this group are not significantly different from those for the Saudi group. Table 1 shows that the respondents who were single were statistically significantly more aware and willing to sign a donor card than were other respondents from other marital

TABLE 1. Respondents' attitude toward kidney donor card related to demographic characteristics.

Demographic	Respondents' attitude			Total	P value
	Willing	Not willing	Unsure		
<i>Age (yr)</i>					
> 20	80(50%)	61(38%)	18(11%)	159	0.00092
20–	173(56%)	113(36%)	25(8%)	311	
30–	73(59%)	35(28%)	16(13%)	124	
40 +	71(45%)	53(33%)	35(22%)	159	
<i>Sex</i>					
Male	268(56%)	171(36%)	42(9%)	481	0.00015
Female	129(47%)	91(34%)	52(19%)	272	
<i>Nationality</i>					
Saudi	349(53%)	225(34%)	81(12%)	655	0.72 NS
Non-Saudi	48(49%)	37(38%)	13(13%)	98	
<i>Marital Status</i>					
Single	178(56%)	116(37%)	24(8%)	318	0.00023
Married	209(51%)	140(34%)	60(15%)	409	
Divorced	3(43%)	2(29%)	2(29%)	7	
Widow	7(37%)	4(21%)	8(42%)	19	
<i>Occupation</i>					
Unemployed	7(47%)	2(13%)	6(40%)	15	0.00001
Housewives	36(39%)	25(27%)	31(34%)	92	
Students	123(55%)	82(37%)	17(8%)	222	
Skilled laborers	20(65%)	6(19%)	5(16%)	31	
Nonskilled laborers	5(56%)	1(11%)	3(33%)	9	
Administrators	57(56%)	42(41%)	3(3%)	102	
Teachers	62(45%)	60(44%)	16(12%)	138	
Military	80(65%)	35(28%)	9(7%)	124	
Businessmen	4(31%)	6(46%)	3(23%)	13	
<i>Education level</i>					
Illiterate	21(34%)	15(25%)	25(41%)	61	0.00001
Elementary	35(45%)	26(34%)	16(21%)	77	
Intermediate	56(69%)	16(20%)	9(11%)	81	
Secondary	112(50%)	89(40%)	21(10%)	222	
University	173(55%)	116(37%)	23(7%)	312	

NS = not statistically significant.

categories ($P < 0.0001$). Respondents who engaged in skilled labor and military personnel were more aware and more willing to sign the donor card than were administrators and teachers. As the level of education increased, the tendency to sign a donor card and the degree of awareness also increased, although there was a peak for those with an intermediate level of education regarding willingness. Of the students interviewed, 55% indicated a willingness to donate through a donor card.

The result also showed that only 18.25% of the respondents had access to a kidney donor card. The younger age groups (those below 40 years of age) appear to have better access to donor cards

than do the higher age groups. Twenty-two percent of the males had better access to a card as compared with 13% of the females; the difference in proportions is statistically significant at $P < 0.05$. Also non-Saudis had better access to a donor card, but this did not show statistical significance ($P > 0.05$). The single subjects, students, military personnel, and administrators appear to have better access than do other occupational groups ($P > 0.2$). However, as the level of education increased, the accessibility to a donor card also increased significantly ($P < 0.05$).

Table 2 shows the general attitude of the respondents toward the kidney donor card. If the percentage of those willing to donate a kidney is

TABLE 2. Overall attitudes toward cadaveric organ donation.

Cadaver donation	No. of respondents	% of Total
KDC delivered to him	70	9.3
KDC sought by him	6	0.8
Don't have but willing	321	42.6
Total of willing respondents	397	52.7
Don't want KDC	262	34.8
Unsure	94	12.5
Total	753	100

KDC = kidney donor card.

added to those who already possess one, the overall proportions of those willing to donate a kidney would increase to 52.7%. An assessment of the respondents' attitudes toward living related donation according to their demographic characteristics showed that there was no differential effect of age, sex, marital status, nationality, occupation, and education in their willingness to donate kidneys during life. Although divorcees were few in this study, they appeared to be less willing than other marital groups to sign a card. The illiterate respondents also appear less willing than other educational groups ($P > 0.5$).

The association between a willingness to sign a donor card and to be a living related donor, examined by the chi-square test, is statistically significant at $P < 0.05$. Forty-two percent of the respondents were both willing to sign a donor card and willing to donate during life. Only 10.6% of the respondents were neither willing to sign a donor card nor to donate during life. They gave reasons such as fear of mutilation, hastiness of organ removal, uncertainty about religious views, and lack of information about kidney donation. Of the total respondents, 10.2% were willing to sign a donor card, but not ready to volunteer as a living related donor; 24% were willing to be a living related donor but not willing to sign a donor card. Two thirds ($N = 64$) of those who were not aware of kidney donor cards ($N = 94$) were willing to donate during life. Only five respondents were unsure about their attitude toward being a living related donor. More than half of the respondents (56.3%) recommended patients in need of transplant should have it done in Saudi Arabia. However, some respondents preferred the U.S. or Europe (5.3%), and India (6.5%). The remaining 31.9% preferred not to commit themselves.

Discussion

The high response rate of 94.1% in this study may be an indication of the interest of the study population in the issue of kidney donations. However, this could be related to the fact that the study sample consisted mostly of educated young individuals below 40 years of age. This study sought the opinions of potential donors, who are usually young, educated, and well informed. The literacy rate of this sample was higher, at 92%, than is seen in the general population. The expected relationship between education, attitude toward organ donation, and accessibility to kidney donor cards is demonstrated in this study. What is striking is that beyond the intermediate level of education the willingness to sign a donor card remains more or less the same. On the other hand, the level of awareness of donor cards continues to increase as the people attain higher educational levels.

The nonsignificant difference found between Saudis' and non-Saudis' attitudes concerning willingness and awareness of kidney donor cards, living related donation, and accessibility to donor cards may reflect general human behavior. It may appear conflicting that there was a higher proportion of people willing to be living related donors than to sign a donor card. However, the strong family ties in Saudi Arabian culture can readily explain this situation. Furthermore, respondents are clearer in their attitudes toward live related kidney donation than to signing donor cards, as only 0.7% of the respondents, compared with 12.5%, respectively, did not commit themselves.

Those respondents who are neither willing to sign a donor card nor donate during life, and who formed a small proportion of the sample, gave reasons similar to those reported in Western studies [5]. However, the finding that 12.5% of the respondents are not aware of donor cards may suggest that health education programs are necessary. The disparity in the reported percentage of respondents who have signed a donor card and the general percentage willing to sign is striking. This could also be a result of apparently poor health education programs on this issue, as well as a lack of a suitable, acceptable, and accessible system for obtaining donor cards.

The fact that males have better access to donor cards than do females could also be attributed to

their better level of education. Culturally, males have more social contact and awareness of public matters and services. The nonstatistically significant differences found regarding accessibility to donor cards between the different age, nationality, marital status, occupation, and education groups is surprising. However, despite the poor access to kidney donation cards, the public attitude toward kidney donation revealed in the present study is comparable to the findings from Western studies [6-8]. Public attitudes toward organ donation in the West were shown to be influenced by culture and religion [7]. Various countries have tried to improve procurement of organ donation and improve accessibility to donor cards through legislative efforts. In the U.S. a driving license can serve as both a donor card and as permission to drive. This is optional but expanding in use. This practice looks attractive but requires time to accurately assess its real outcome. In many European countries, a presumed consent (implied consent) law is applicable. Considerable criticism in these countries has been encountered with increasing insistence on written consent from the donors [6]. The implied consent concept and the sale of organs for transplantation are not acceptable in Saudi culture. Recently, the senior Moslem authorities (Ulama) consented to surgeons' performing transplant operations, provided written consent from the donor or his/her next of kin is secured [9,10].

The majority of the respondents (56.3%) expressed their confidence and satisfaction in the transplant facilities in the Kingdom of Saudi Arabia. It should be borne in mind that attitudes change over time, and there is a gap between how people in surveys indicate what they desire and what they actually do in a real situation. Publicity relating to kidney donation needs to be continued.

Programs that lower professional and system barriers erected against organ donation are very much needed. Health professionals, particularly those working in hospitals, can help by adopting a more aggressive approach to seeking consent for organ donation.

Acknowledgment

I would like to thank the following colleagues, namely Prof. El-Shabrawy Ali, Prof. Abu Aisha, Dr. Bamgboye, Dr. Hussein I, and Dr. Khadir, for their help in the preparation of the manuscript. Thanks are also expressed to Mrs. Teresita E. Aliling for secretarial help.

References

1. Unpublished data, National Kidney Foundation in Saudi Arabia, 1989.
2. National Kidney Foundation Bulletin. Management of ESRD patients in the Kingdom of Saudi Arabia. 1987;1(2):3-8.
3. Abomelha MS, Al-Khader AA, Jawdat M, et al. Logistical implications in the importation of cadaveric organs. In: Proceedings of the 2nd International Middle East Symposium on Organ Transplantation, Riyadh Armed Forces Hospital, Saudi Arabia. 1984;34-6.
4. Abomelha MS, Al-Khader AA, et al. Experience of renal transplantation at Riyadh Armed Forces Hospital, Saudi Arabia. In: Proceedings of the 2nd International Middle East Symposium on Organ Transplantation, Armed Forces Hospital, Riyadh, Saudi Arabia. 1984;34-6.
5. Corlett S. Public attitudes toward organ donation. *Transplant Proc* 1985;17(6,suppl 3):103-10.
6. Gebel H, Lindsough K. A survey of public attitudes toward cadaveric organ donation in a Swedish community. *Transplant Proc* 1988;22(3):431.
7. Manninen DL, Evans RW. Public attitudes and behavior regarding organ donation. *JAMA* 1985;253(21):3115.
8. Al-Faqih S. Effect of knowledge and Islamic religion on public attitude toward kidney donation in Riyadh, Saudi Arabia (unpublished data).
9. Al-Otobi K, Al-Khader A, Abomelha M. The first Saudi cadaveric kidney transplantation. *Saudi Med J* 1985;(3):217-23.
10. The senior ulama decree no 99, dated 6/11/1402 H (1982 AD) which encourages organ donation (Arabic).

Case Reports

PNEUMONIA DUE TO *SALMONELLA* TYPHIMURIUM

Mohammed Azher, MRCP; Faisal El-Kassimi;
Abdul Hamid Chagla, PhD

Salmonellosis is primarily an intestinal infection. Extraintestinal invasion by the organism is rare and mainly occurs in immunocompromised hosts. Endocarditis, epidural abscess, brain abscess, and splenic abscess have been reported in this context [1-5]. *Salmonellae* are a very rare cause of pneumonia, even in immunosuppressed patients [4]. We report a case of bronchopneumonia caused by *Salmonella typhimurium* in a patient with systemic lupus erythematosus (SLE) and pulmonary fibrosis.

Case Report

A 25-year-old woman was admitted with diarrhea and fever of one week's duration. She had no abdominal pain or blood in her stools. Three days after admission, cough and expectoration of mucopurulent sputum developed. She was known to have SLE accompanied by fibrosing alveolitis and chronic respiratory failure, for which she had been taking oral prednisolone for the previous 2 years. The dose of steroids had been gradually tapered, but she had been taking 20 mg of prednisolone for one month before admission.

Examination revealed a febrile woman (39.5°C) with a pulse rate of 120/min, cyanosis, and tachypnea (respiratory rate, 40/min). Chest examination showed bilateral basal inspiratory and expiratory crackles. Abdominal and rectal examination findings were normal. Her biochemistry and blood pictures were normal

(white cell count, 8.8×10). Arterial blood gas values while breathing room air were: PaO₂, 40 mm Hg (PaO₂ before this illness was approximately 60 mm Hg); PaCO₂, 34 mm Hg; pH, 7.35; and HbO₂ saturation, 76%. Chest x-ray study showed bronchopneumonic shadows in both lung bases superimposed on an old micronodular infiltrate of pulmonary fibrosis. *Salmonella typhimurium* was grown from both sputum and blood on several occasions and organisms from both sites had identical biochemical and serological profiles. Her stool cultures on three separate occasions were negative for *Salmonella*.

The patient was successfully treated with intravenously administered ampicillin, oxygen inhalation, and chest physiotherapy. Her blood gas values and chest x-ray appearance returned to baseline after three weeks of treatment. Her stools were repeatedly negative for salmonellae and there was no evidence of gallbladder disease before or after the illness.

The isolates from sputum as well as blood culture were identified as *S. typhimurium* based on their growth characteristics (i.e., non-lactose-fermenting colonies on MacConkey's agar), biochemical profile using the Analytical Profile Index (API-system), and slide serological tests. The antibiogram showed that the organism was sensitive to ampicillin, cotrimoxazole, gentamicin, chloramphenicol, and erythromycin.

Discussion

Salmonellosis is primarily an intestinal infection but there have been rare reports of extraintestinal spread [1-5]. *Salmonella* pneumonia is very rare even in immunosuppressed individuals [6,7]. Canney et al [8] reported on one patient with this condition who was receiving chemotherapy for non-Hodgkin's lymphoma. Gratten et al [9] from Papua-

From the Departments of Medicine (Drs. Azher, El-Kassimi) and Microbiology (Dr. Chagla), College of Medicine, King Saud University, Riyadh.

Address reprint requests and correspondence to Dr. Azher: Department of Medicine (38), College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Accepted for publication 29 July 1990.

New Guinea described four pre-school children with *Salmonella* pneumonia due to *S. choleraesuis* and attributed these cases to contact with pigs.

In the patient reported here, the underlying predisposing factors were corticosteroid therapy and the SLE. *Salmonella* bacteria are facultative intracellular organisms, the main host defense mechanism for such infections being mediated by cellular immunity and macrophage activity. It is possible that our patient may have possessed a defect in cellular immunity due to SLE and that combined with the corticosteroid treatment may account for the association with this type of infection.

The influence of pulmonary fibrosis in the development of bronchopneumonia is not entirely clear. It has been postulated that patients with pulmonary fibrosis are more prone to pulmonary infections as a result of defective mucociliary clearance and disturbed tissue macrophage function [10].

Although our patient gave a history of mild diarrhea, some patients may not have any gastrointestinal symptoms [11]. This may reduce the index of suspicion of salmonellosis, especially in areas of low endemicity. In immunosuppressed patients, the mortality from *Salmonella* infections is approximately 10%; therefore, the early use of appropriate antibiotics is mandatory.

We recommend that patients with pneumonia who live in tropical areas where there is a high incidence of *Salmonella* infection should be carefully evaluated for this organism, especially if they are

immunocompromised or have underlying pulmonary fibrosis.

Acknowledgment

We are grateful to Ms. Bennie Campos and Ms. Mimi S. Gurrea for their secretarial assistance in typing the manuscript.

References

1. Mokhobo KP. Typhoid cardiac involvement. *S Afr Med J* 1975;49:55-6.
2. Herbert DA, Ruskin J. *Salmonella typhi* epidural abscess occurring 47 years after typhoid fever. *J Neurosurg* 1982;57:719-21.
3. Kager PA, Rietra PJGM. Splenic abscess due to *Salmonella typhi*. *Trop Geogr Med* 1982;34:375-7.
4. Penaloza JL, Llansas A, Kumate J. Pyogenic liver abscess caused by *Salmonella typhi*. *Bol Med Hosp Infant Mex* 1974;31(5):917-24.
5. Boeckers M, Kortling GW. Cutaneous abscess caused by *Salmonella typhimurium*. *Med Welt* 1982;33(10):345-6.
6. Samra Y, Shaked Y, Maier MK. Non-typhoid salmonellosis in renal transplant recipients: report of five cases and review of the literature. *Rev Infect Dis* 1986;8(3):431-40.
7. Sinkovics JG, Smith JP. Salmonellosis complicating neoplastic disease. *Cancer* 1969;24:631-6.
8. Canney PA, Larsson SN, Hay JH, Yussuf MA. Case report: salmonella pneumonia associated with chemotherapy for non-Hodgkin's lymphoma. *Clin Radiol* 1985;36(5):459-60.
9. Gratten M, Barker J, Rongap A. Pneumonia due to *Salmonella choleraesuis* in infants in Papua New Guinea (letter). *Lancet* 1983;2:580-1.
10. Fishman AP. *Pulmonary diseases and disorders*, ed 2. New York: McGraw Hill, 1988;720.
11. Olutola PS, Familusi JB. *Salmonella typhi* pneumonia without gastrointestinal manifestations. *Diagn Imag Clin Med* 1985;54(5):263-7.

INTRACTABLE DIARRHEA DUE TO WHIPPLE'S DISEASE IN A SAUDI: REPORT OF A CASE AND LITERATURE REVIEW

Dharmaraj H. Patil, MRCP(UK);
Eric S. Boye, FRCPC

Whipple's disease is a rare systemic disorder that can affect virtually any organ in the body. The small intestine is involved in the vast majority of patients. The disease has been reported most frequently in Caucasians but there have been a few cases reported in other races [1,2]. As far as we are aware, there have been no reports of Whipple's disease in Saudis. We report a case of Whipple's disease in a patient from the Al-Baha area located in southwestern Saudi Arabia.

Case Report

A 50-year-old male Saudi farmer from Qunfudah on the Red Sea coast presented with a history of diarrhea of four years' duration. Prior to the onset of diarrhea he had been well and had undergone no form of abdominal surgery. He complained of passing three to five stools a day; these were pale, semisolid to watery in consistency and had an offensive odor. There was no history of rectal bleeding. He also complained of anorexia and occasional vomiting. Since the start of the diarrhea, he had gradually lost weight and become emaciated. In addition to the diarrhea and vomiting, he had vague abdominal discomfort but had not experienced severe abdominal pain at any time. He had been to several hospitals during the four years and had undergone several investigations, but according to him, no definite diagnosis had been made and he had not benefited from any of the treatments. Instead his condition had steadily worsened and he had been bedridden

for about a month before being brought to this hospital.

On examination the patient looked moribund. He was markedly cachectic, dehydrated, and pale. He had no significant lymphadenopathy and was afebrile. He had moderate bilateral leg edema. His blood pressure was 90/60 mm Hg with a pulse of 90/min. Respiratory, cardiovascular, and neurological findings were all normal. The abdomen was soft with no organomegaly, tenderness, or ascites. Bowel sounds were normal. Initial laboratory investigations revealed a low hemoglobin content (91 gm/L) and mean corpuscular volume (68.5 fL). His serum albumin (17 gm/L) and total protein (40 gm/L) levels were also low and serum calcium concentration (1.9 mmol/L) was in the low normal range. Apart from a positive stool for occult blood, all other laboratory investigations, including prothrombin time and stool microscopy and cultures, were normal. The Mantoux test was negative.

His chest x-ray was normal but a plain x-ray of the abdomen showed a few gas-fluid levels with moderate dilatation of the small bowel. Upper abdominal ultrasound examination was normal. Barium meal and follow-through examination revealed slow transit of barium through the small intestine. There was dilatation of loops of small bowel with flocculation of the barium. These changes are consistent with malabsorption syndrome. Abdominal computed tomographic scans showed no abnormality apart from dilated loops of small intestine. An echocardiogram was normal.

Endoscopy revealed that the duodenal mucosal folds were edematous, friable, and covered with small yellowish waxy nodules. Endoscopic duodenal biopsies revealed a flat duodenal mucosa showing pronounced infiltration of

From the Departments of Internal Medicine and Pathology, King Fahad Hospital, Al-Baha.

Address reprint requests and correspondence to Dr. Patil: Department of Internal Medicine, King Fahad Hospital, P.O. Box 204, Al-Baha, Saudi Arabia.

Accepted for publication 30 July 1990.

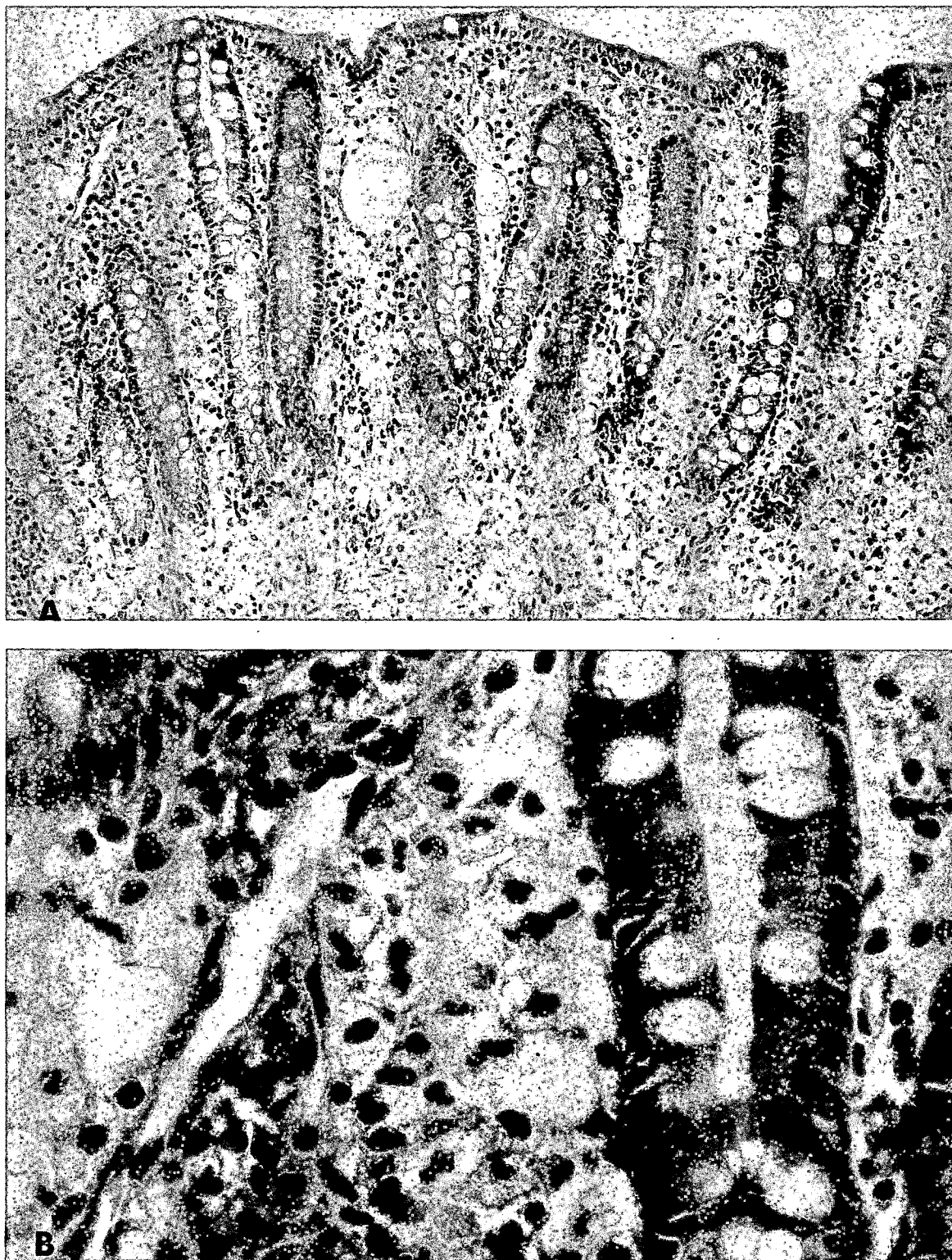


FIGURE 1. Endoscopic duodenal biopsy specimen showing flat mucosa (total villous atrophy), abundant large, pale-staining cells, and clear spaces of variable size within the lamina propria. (H&E; [A] $\times 50$; [B] $\times 200$, before reduction.)

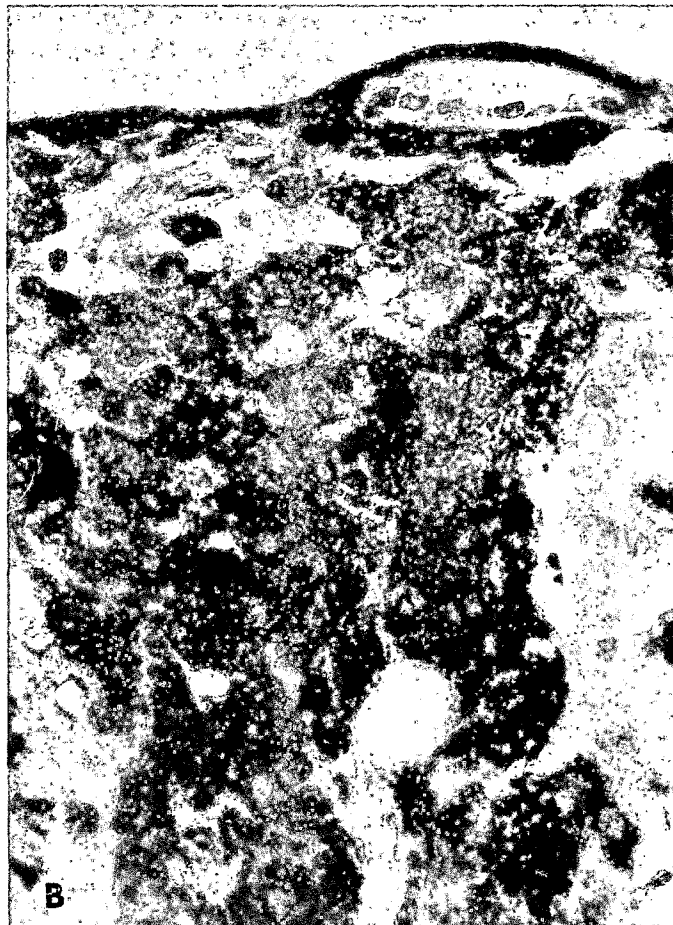


FIGURE 2. Periodic acid-Schiff (PAS)-positive macrophages (darkly stained) in the lamina propria in a duodenal biopsy specimen exposed to diastase digestion. (H&E; [A]×50; [B]×200, before reduction.)

the lamina propria by large mononuclear cells with abundant pale, foamy cytoplasm. There were also scattered clear spaces of variable sizes within the lamina propria (Figure 1). The foamy cells extended through the muscularis mucosae into the submucosa. They contained abundant periodic acid-Schiff (PAS)-positive granules that were resistant to diastase digestion (Figure 2). The PAS-positive granules were also free in the lamina propria. Sections stained by the Ziehl-Neelson technique did not reveal any acid-fast bacilli. These histological findings are characteristic of Whipple's disease. Rectal biopsies also showed the PAS-positive foamy cells within the rectal mucosa. A subsequent duodenal aspirate, stained by the PAS technique, revealed similar PAS-positive macrophages in the duodenal fluid. We are not aware that this last finding has been reported by other workers. However, PAS-positive macrophages have been found in the cerebrospinal fluid of patients with cerebral Whipple's disease [3,4]. Their value in the diagnosis of intestinal Whipple's disease has not been assessed.

The patient was initially treated with crystalline penicillin (1 megaunit 6 hourly for 11 days) and then penicillin V (500 mg 6 hourly for 5 days). Orally administered tetracycline (500 mg 6 hourly for 4 weeks) was started at the same time. Subsequently he was given trimethoprim-sulfa (two tablets twice daily) to be continued for one year.

Within a week of starting antibiotic treatment there was dramatic clinical improvement, with complete cessation of diarrhea. His appetite improved greatly and he became ambulatory after two weeks' therapy. He was discharged home in satisfactory condition.

Four weeks after discharge, the patient was readmitted with vomiting and diarrhea of 2 days' duration. This resolved with symptomatic treatment alone. However, during this admission he suffered an acute myocardial infarction with congestive cardiac failure, from which he recovered. Repeat endoscopy with biopsy done six weeks after starting antibiotics showed no significant improvement in the duodenal mucosa, endoscopically or histologically. At a recent review he was well and had gained weight. There has been marked improvement in his hematological and biochemical profile.

Discussion

Whipple's disease is a rare systemic disease that can affect many organs but presents predominantly with gastrointestinal symptoms. It was first described in 1907 by George Whipple, an American pathologist, who called it "intestinal lipodystrophy" [5]. Until 1988 only 741 cases had been reported worldwide [6]. It is thought to occur predominantly in Caucasians [1,2]. We believe that this is the first report of Whipple's disease in a Saudi national. A review of the *Saudi Medical Bibliography* from 1887 to 1986 revealed no reports of the disease [7]. A further search of Saudi medical publications up to June 1990 similarly failed to unearth any reports.

Nearly 85% of the patients are male, with an average age of 50 years at the time of diagnosis. Clinical presentation varies but the main presenting features are malabsorption with diarrhea and weight loss, as was the case in our patient. Fever, skin pigmentation, anemia, generalized lymphadenopathy, arthritis, pleurisy, pericarditis, myocarditis, valvular endocarditis, glomerulonephritis, and central nervous system manifestations occur in some patients and may occasionally be the presenting features. The affected organ or tissue is infiltrated by large mononuclear phagocytes containing granular, diastase-resistant, PAS-positive material.

The small intestine is invariably involved and diagnosis is usually made based on small intestinal biopsy findings. Barium studies are usually abnormal [8], the most characteristic feature being marked thickening of the mucosal folds, especially in the duodenum and proximal jejunum. Dilatation of the small bowel, as seen in our patient, is unusual but has been described. Endoscopy reveals thickened duodenal mucosal folds covered by miliary, yellowish, waxy nodules [9,10], as seen in our patient. The nodules may become confluent and even form plaques.

Histologically there is broadening and stunting of the villi, and in severe cases, there may be subtotal or total villous atrophy resulting in a flat mucosa (see Figure 1). The most striking feature is the presence of numerous large foamy macrophages within the lamina propria. These contain abundant granular PAS-positive material, as previously noted. Small numbers of these cells may be seen in the submucosa. Small 1 to 2 μ m

bacillary organisms have been identified in the mucosa by electron microscopy [10–12] but these have not yet been cultured. They occur freely in the lamina propria as well as within the large foamy macrophages. They are believed to be the causative agent and they disappear after 4 to 8 weeks of antibiotic treatment [1]. The other histological finding in the intestinal mucosa is the presence of variably sized clear spaces that contain lipid (see Figure 1) [10]. PAS-positive mononuclear phagocytes also occur in the colonic mucosa and in other affected organs. The finding of these cells in the colonic mucosa alone cannot be used to diagnose Whipple's disease, as muciphages and macrophages containing lipofuscin have a similar appearance.

Similar PAS-positive cells have been described in the intestinal mucosa of AIDS patients with *Mycobacterium avium intracellulare* infection [13,14]. They can be distinguished with acid-fast stains. An enzyme-linked immunosorbent assay for human immunodeficiency virus on the serum of our patient was negative and there were no acid-fast bacilli in the biopsies. The mesenteric lymph nodes may, in addition, show small non-caseating granulomas. The finding of PAS-positive macrophages in *M. avium* infections in AIDS patients, together with the finding of a helper T-cell deficiency [15], monocyte/macrophage abnormalities [16,17], and a lack of immunoglobulin-containing cells in the intestinal mucosa of some patients with Whipple's disease [18], have led to the suggestion that clinical Whipple's disease may result from an immunological deficit causing defective macrophage destruction of the engulfed causative bacteria.

Whipple's disease bacilli have been identified in the walls of blood vessels in various organs and may be associated with vasculitis and intimal hyperplasia [19–21]. Our patient's myocardial infarction was presumably a consequence of his Whipple's disease and may have resulted from coronary arteritis with thrombosis.

Most of the biochemical and hematological abnormalities found in Whipple's disease are related to severe intestinal malabsorption. Depending on the severity, there may be steatorrhea, hypocalcemia, hypomagnesemia, hypoalbuminemia, and anemia due to deficiencies of various nutritional factors.

Whipple's disease is a curable condition, but all patients will die if it is not detected and treated effectively. Treatment with antibiotics produces a prompt and dramatic relief of symptoms in most patients. The morphological changes, however, take much longer to abate. Various antibiotics have been shown to be effective, but must be given for a long time otherwise there may be relapse. There are no controlled trials to show which antibiotic is the best and for how long it must be given. However, because brain involvement is life-threatening, the choice should include drugs that cross the blood-brain barrier. In a recently published retrospective study of 88 patients, Keinath et al [22] found that the use of a single antibiotic was associated with a higher relapse rate than the use of two or three. They recommend that penicillin and streptomycin be given for two weeks followed by trimethoprim-sulfa for one year. Relapses should be treated like new cases, and except for patients with central nervous system involvement, patients respond well.

Acknowledgment

We thank Dr. Ionel Bucur, consultant haematologist, and Mrs. Cleo Erwin, Librarian, King Fahad Hospital, Al-Baha; Miss Betty P. Lange, Senior Editor, *Annals of Saudi Medicine*; and Dr. M. B. Satti, Associate Professor of Pathology, King Faisal University, Dammam, for assisting us with the literature search.

References

1. Dobbins WO III. Whipple's disease. Springfield, Ill: Thomas, 1987.
2. Comer GM, Brandt LJ, Abissi CJ. Whipple's disease: a review. *Am J Gastroenterol* 1983;78:107-14.
3. Wietholter H, Dichgans J. Diagnosis of cerebral Whipple's disease by cerebrospinal fluid cytology. *Arch Psychiatr Nervenkr* 1982;231(3):283-7.
4. Leger JM, Sauron B, Rousseau P, Gray F. Whipple's disease with encephalopathy: a case report with review of the literature. *Rev Neurol (Paris)* 1983;139(5):375-9.
5. Whipple GH. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. *Bull Johns Hopkins Hosp* 1907;19:382-91.
6. Dobbins WO III. Whipple's disease. *Mayo Clin Proc* 1988;63:623-4.
7. Madkour MM, Kudwah AJ. Saudi Medical Bibliography, 1887–1980; 1981–82; 1983–84; 1986. Edinburgh: Churchill Livingstone, 1983, 1986.
8. Philips RL, Carlson HC. The roentgenographic and clinical findings in Whipple's disease. *Am J Roentgenol Rad Ther Nucl Med* 1975;123:269.

9. Reiman JF, Rosch W. Synopsis of endoscopic and related morphological findings in Whipple's disease. *Endoscopy* 1978;10:98.
10. Morson BC, Dawson IMP, Day DW, et al. *Morson & Dawson's gastrointestinal pathology*, ed 3. Oxford: Blackwell, 1990;257-8.
11. Dobbins WO III, Kawanishi H. Bacillary characteristics in Whipple's disease: an electron microscopic study. *Gastroenterology* 1981;80:1469.
12. Silva MT, Macedo PM, Nunes JF. Ultrastructure of bacilli and the bacillary origin of the macrophage inclusions in Whipple's disease. *J Gen Microbiol* 1985;131(Pt.5):1001-13.
13. Billen JS, Urmacher C, West R, Shike M. Disseminated *Mycobacterium avium intracellulare* infection in acquired immune deficiency syndrome mimicking Whipple's disease. *Gastroenterology* 1983;85(5):1187-91.
14. Roth RI, Owen RL, Keren DF, Velberding PA. Intestinal infection with *Mycobacterium avium* in acquired immune deficiency syndrome (AIDS). Histologic and clinical comparison with Whipple's disease. *Dig Dis Sci* 1985;30(5):497-504.
15. Gras C, Kaplanski S, Farnarier C, et al. Immunological profile of Whipple's disease evolving over a period of 17 years. *Ann Med Interne (Paris)* 1988;139(1):24-8.
16. Bjerknes R, Laerum OD, Degaard S. Impaired bacterial degradation by monocytes and macrophages from a patient with treated Whipple's disease. *Gastroenterology* 1985;89(5):1139-46.
17. Bjerknes R, Odegaard S, Bjerkvic R, et al. Whipple's disease: demonstration of a persisting monocyte and macrophage dysfunction. *Scand J Gastroenterol* 1988;23(5):611-9.
18. Stoinov SG, Nikolov NP, Todorov DM, et al. Whipple disease: clinical and immunohistologic findings in 2 cases. *Dtsch Z Verdau Stoffwechselkr* 1984;44(5):232-40.
19. James TN, Bulkley BH. Abnormalities of the coronary arteries in Whipple's disease. *Am Heart J* 1983;105(3):481-91.
20. James TN, Bulkley BH. Vascular lesions of the gastrointestinal system in Whipple's disease. *Am J Med Sci* 1984;288(3):125-9.
21. James TN, Bulkley BH. Whipple bacilli within the tunica media of pulmonary arteries. *Chest* 1984;86(3):454-8.
22. Keinath RD, Merrel DE, Vlietstra R, et al. Antibiotic treatment and relapse in Whipple's disease: long-term follow-up of 88 patients. *Gastroenterology* 1985;88(6):1867-73.

HODGKIN'S DISEASE INVOLVING THE URINARY BLADDER: A CASE REPORT

Ezzeldin M. Ibrahim, FRCPI; Mohammad B. Satti, MRCPATH
Osama M. Koreich, DMRT, FRCR; Issa A. Al-Uqali, MB,BS
Fatma A. Al-Mulhim, MB,BS

More than 155 years have elapsed since Thomas Hodgkin first described a disease of the lymphoid system that was later to bear his name [1]. Since then, many facts about Hodgkin's disease (HD) have been made known. Despite this, the spread pattern of the disease is still considered enigmatic. Two distinctively different mechanisms have been proposed: the "contiguity" [2] and the "susceptibility" [3,4] theories. Perhaps both theories combined can explain certain aspects of the disease. For instance, subdiaphragmatic HD is a rare clinical presentation that occurs in only 3 to 10% of the patients [5,6], but disease relapse of subdiaphragmatic primary disease occurs predominantly above the diaphragm [5,6]. We encountered a case of subdiaphragmatic presentation of HD with later subdiaphragmatic relapse to the urinary bladder, a rare site for secondary involvement.

Case Report

A 65-year-old Saudi man was admitted to our hospital in October 1988 with a 6-week history of frequency of urination, nocturia, and severe suprapubic pain on voiding. Clinical findings were unremarkable apart from the presence of a palpable urinary bladder and enlarged firm prostate. Urinary catheterization drained only a few milliliters of residual urine.

Previously the patient had had clinical stage 1A

mixed-cellularity HD, involving a single 2×2 -cm left inguinal lymph node, diagnosed in August 1987. Thorough clinical staging revealed negative findings. The patient was given 4,000 rads of radiotherapy over a four-week period as an inverted-Y field to the subdiaphragmatic lymph node regions. Extensive restaging was done in January and July 1988 and showed no evidence of relapse. The patient remained asymptomatic and in remission until August 1988 when he was investigated because of impotence. Rectal examination revealed an enlarged prostate. Computed tomographic (CT) scan of the pelvis showed an infiltrate in the right lateral bladder wall (Figure 1A). The patient refused cystoscopy until a later presentation in October 1988. Laboratory tests, bone marrow aspiration and biopsy, chest roentgenogram, bilateral pedal lymphangiography, and CT scan of the chest and abdomen were all normal. Pelvic CT scan showed further progression of the growth within the urinary bladder (Figure 1B). Furthermore, magnetic resonance imaging showed global bladder infiltration without evidence of any other pelvic disease (Figure 2). Cystoscopy was done and showed mucosal hyperemia.

Histological examination of multiple bladder biopsy specimens showed denuded epithelium and underneath a mixed infiltrate formed of numerous eosinophils, lymphocytes, plasma cells, and large mononuclear cells (Figure 3). Occasional typical Reed-Sternberg cells were identified (Figure 4), confirming the diagnosis of HD of mixed-cellularity type. The infiltrate also extended into the muscle layer. Therapy was initiated using systemic combination chemotherapy.

From the College of Medicine and Medical Sciences, King Fahd University, Dammam.

Address reprint requests and correspondence to Dr. Ibrahim: King Fahd Hospital of the University, Al-Khobar, P.O. Box 40004, Al-Khobar 31952, Saudi Arabia.

Accepted for publication 30 July 1990.

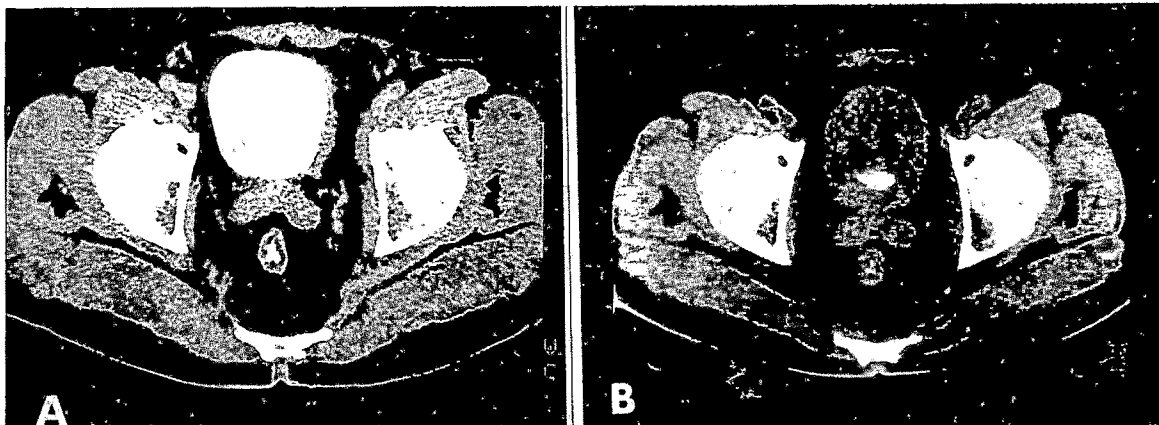


FIGURE 1. (A) Computed tomographic scan showing a rim-like growth within the lateral wall of the urinary bladder. The prostate is also bulky (August 1988). (B) More extensive growth is seen within the urinary bladder, almost obliterating the lumen with multiple areas of attenuation (October 1988).



FIGURE 2. Coronal T_1 magnetic resonance imaging scan showing homogeneous involvement of the urinary bladder by a soft tissue mass. There is no other evidence of pelvic disease.

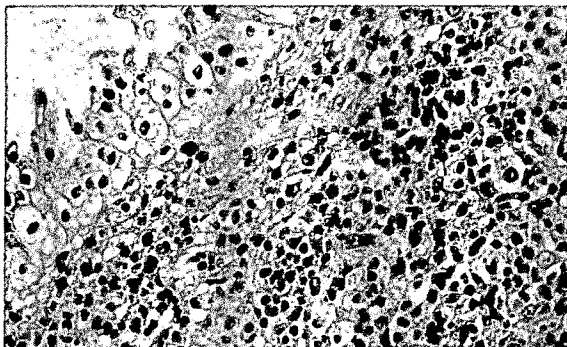


FIGURE 3. Bladder mucosa infiltrated by a mixture of lymphoid, mononuclear cells, and eosinophils. (H&E; original magnification, $\times 325$.)

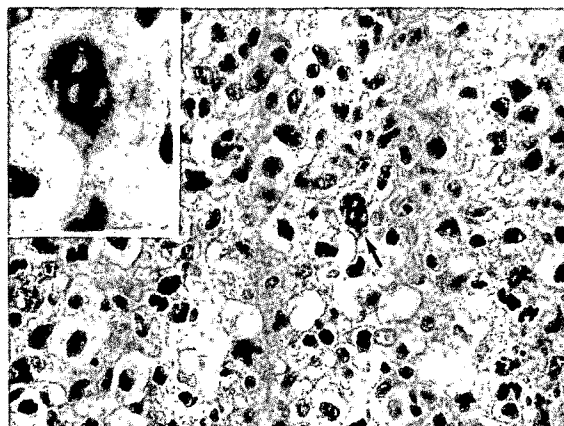


FIGURE 4. Detail of the infiltrate seen in Figure 3. A Reed-Sternberg cell is indicated by an arrow (H&E; original magnification, $\times 1125$.)

Discussion

Subdiaphragmatic HD is a rare entity that occurs in 3 to 10% of patients [5,6]. In five large combined series, the most common presentation of subdiaphragmatic HD was peripheral inguinal, femoral, or superficial iliac lymphadenopathy, constituting approximately 80% of all cases [5]. While primary urinary bladder HD or non-Hodgkin's lymphoma has been described previously [7-9], secondary involvement, particularly with HD, has been reported rarely [10,11]. In an autopsy series [10], HD involved the bladder in 4% of the cases that occurred in association with disseminated disease, causing urinary symptoms in only 13% of patients. A case report described urinary bladder relapse of HD ten years after

mantle radiation therapy, given in a patient with CS I supradiaphragmatic disease [11]. In this latter report, the diagnosis was established initially in a urine specimen using exfoliative cytology. Our case represents another instance of this unusual relapse pattern. In both cases the urinary bladder was apparently the only site of HD relapse.

It is conceivable that the bladder disease in our patient resulted from direct extension from an involved pelvic lymph node outside the radiation therapy portals. However, lack of clinical or radiological evidence of pelvic disease at presentation, during more than one year of follow-up, and at relapse probably rules out such a contiguity pattern of spread [2]. The theory of hematogenous spread as proposed by Smithers [3,4] might explain the bladder relapse without disease documentation elsewhere. Lack of evidence of vascular invasion in the groin node or in the bladder biopsy specimens does not rule out the possibility of bloodstream spread of HD from the primary site. Lamoureux et al [12] found no evidence of vascular invasion in the original biopsy material in patients who had regionally localized HD and in whom extranodal dissemination subsequently developed following primary radiotherapy.

Our case illustrates an unusual pattern of relapse of HD from initially localized subdiaphragmatic disease. With more patients now achieving long-term survival, previously uncommon complications may become more clinically important. Urinary bladder involvement, though

uncommon, should be suspected if there is clinical and/or radiological evidence that suggests its presence.

References

1. Hodgkin T. On some morbid appearance of the absorbent glands and spleen. *Med Chir Trans* 1832;17:68-114.
2. Rosenberg SA, Kaplan HS. Evidence for an orderly progression in the spread of Hodgkin's disease. *Cancer Res* 1966;26:1225-31.
3. Smithers DW. Spread of Hodgkin's disease. *Lancet* 1970;1:1262-7.
4. Smithers DW, Lillicrap SC, Barnes A. Patterns of lymph node involvement in relation to hypotheses about the modes of spread of Hodgkin's disease. *Cancer* 1974;34:1179-86.
5. Krikorian JG, Portlock CS, Mauch PW. Hodgkin's disease presenting below the diaphragm: a review. *J Clin Oncol* 1986;4:1551-62.
6. Leibenhaut MH, Hoppe RT, Varghese A, Rosenberg SA. Subdiaphragmatic Hodgkin's disease: laparotomy and treatment results in 49 patients. *J Clin Oncol* 1987;5:1050-5.
7. Wang CC, Scully RE, Leadbetter WF. Primary malignant lymphoma of the urinary bladder. *Cancer* 1969;24:772-6.
8. Santino AM, Shumaker EJ, Garces J. Primary malignant lymphoma of the bladder. *J Urol* 1970;103:310-33.
9. Aquilina JN, Bugeja TJ. Primary malignant lymphoma of the bladder: case report and review of the literature. *J Urol* 1974;112:64-5.
10. Sufrin G, Keogh B, Moore RH, Murphy GP. Secondary involvement of the bladder in malignant lymphoma. *J Urol* 1977;118:251-3.
11. Bocian JJ, Flam MS, Mendoza CA. Hodgkin's disease involving the urinary bladder diagnosed by urinary cytology: a case report. *Cancer* 1982;50:2482-5.
12. Lamoureux KB, Jaffe ES, Berard CW, Johnson RE. Lack of identifiable vascular invasion in patients with extranodal dissemination of Hodgkin's disease. *Cancer* 1973;31:824-5.

KLINEFELTER SYNDROME, RARE VARIANT 49, XXXXY

Hussein Salman, MD(France); Ahmed Abanamy, MD(France);
Nizzamudin Khan, MBBS, FCPS; Ghassan Basset, DCH;
Afsar H. Choudhury, BSc, MBBS; Mona O. El-Ruby, MSc, PhD

We describe the case of a rare variant of Klinefelter's syndrome with a 49 XXXXY karyotype. This rare form was first described in 1960 and has sufficiently distinctive features (compared with the classic 47 XXY karyotype) to be detected in childhood. Relevant features are compared with those described elsewhere in the literature.

Case Report

A two-year, four-month-old Saudi male was referred to Suleimania Children's Hospital, Riyadh, because of recurrent chest infections and questionable immune deficiency.

Past history revealed the child was born after an eight-month pregnancy with a low birth weight (1.5 kg), followed by delayed milestones (smiled at five months, sat at eighteen months, walked at two years, three months) and delayed speech. He exhibited emotional lability (cried very easily), had had recurrent chest infections, and had had conjunctivitis since six months of age.

The parents were not related; the mother was 35 years old, and the father, 60 years. The seven siblings were normal and healthy.

Growth parameters showed a height below 1.75 -SD, weight below 1 -SD, and normal head circumference.

Examination revealed an immature-looking child showing delayed development, who showed abnormal features such as short neck, upward slanting palpebral fissures, hypertelorism, epicanthal folds, broad nose, kyphosis, and short

incurved fifth finger. Other relevant features included limited elbow pronation, a soft systolic murmur with a loud second sound, and abnormal external genitalia with a very small phallus, undescended small atrophic testes, hypoplastic scrotum, and coronal hypospadias.

Routine blood analysis (complete blood count, erythrocyte sedimentation rate, blood urea nitrogen, blood glucose, electrolytes) and urine test results were all normal. Tuberculin test (10 TU) was negative. Immunoglobulin assays showed normal IgG and IgM, and low IgA. IgG subclasses and cellular and nonspecific immunity were not evaluated. Hormonal blood assays showed a low testosterone level of 0.01 ng/ml (reference interval, 2.4–10.9 ng/ml) with a high follicle stimulating hormone (FSH) level of 31.1 IU/L (reference interval, 1.9–2 IU/L) and normal luteinizing (LH) hormone level of 3.2 mIU/ml (reference interval, 3.13–5 mIU/ml). Human chorionic gonadotropin (HCG) test showed a poor testosterone response (0.09 ng/ml). Luteinizing hormone releasing hormone (LHRH) showed a high FSH response, more so than the LH response. Chromosomal analysis showed a 49 XXXXY karyotype. Electrocardiogram revealed a relatively low-voltage, single ventricular extra systole. Ultrasound examination of the abdomen, echocardiogram, and computed tomographic scan of the brain (previously done in a local hospital) were normal. Skeletal survey showed delayed bone age (1 year), kyphosis, short incurved fifth finger, radioulnar synostosis, shallow acetabulum, and mild right hip dislocation. Chest x-ray study showed mild cardiomegaly. Based on these findings, Klinefelter's syndrome, rare variant 49 XXXXY, was diagnosed. The patient was managed symptomatically and received gammaglobulin intramuscularly for six months.

From the Suleimania Children's Hospital (Drs. Salman, Abanamy, Khan, Basset), Cytogenetic Laboratory (Drs. Choudhury, El-Ruby), Central Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Salman: Suleimania Children's Hospital, P.O. Box 59046, Riyadh 11525, Saudi Arabia.

Accepted for publication 25 August 1990.

Discussion

Klinefelter's syndrome (seminiferous tubular dysgenesis) is a genetic gonadal defect displaying variable phenotypic features related to a sex chromosome complement that includes two or more X chromosomes and one or more Y chromosomes. It is probably the most common human sex chromosomal aberration [1-3]. The 47 XXY complement, the most common pattern in persons with Klinefelter's syndrome, is also the most common cause of male hypogonadism and infertility, occurring in 1 of 750 live born male subjects and in 0.45 to 2.38% of mentally retarded or other children referred to psychiatric clinics. However, diagnosis of the 47 XXY pattern is rare prior to puberty because of the paucity and subtlety of the clinical manifestations in childhood [2-5].

Some cases of Klinefelter's syndrome have mosaic patterns, i.e., 46 XY/47XXY, 46 XY/48 XXXY, 45 X/46 XY/47 XXY, 46 XX/47 XXY. The presence of more than two X chromosomes is rare, with variants such as 48 XXXY, 48 XXYY, 49 XXXYY, 49 XXXXY, and 50 XXXXXY [6].

The 49 XXXXY Klinefelter variant was first described in 1960 [1], and about 40 cases have been recorded since then. This to our knowledge is the first case reported from Saudi Arabia. Considering the pathogenesis, increased maternal age was thought to predispose to meiotic disjunction and to the syndrome, but in most instances, as in our case, maternal age was not advanced.

Most of the clinical features, which are actually quite distinctive, were found in our patient (Table 1), except for malformed ears, strabismus, a depressed nasal bridge, prognathism, and increased frequency of digital arch patterns; however, these features are not always present. The genital anomalies in our patient were typical. Hypospadias is encountered only occasionally. Our patient did not possess the classic skeletal abnormalities (Table 2). The only ones present were radioulnar synostosis, the abnormal ossification centers in the hands (delayed bone age of 1 year for a chronological age of 2 years, 6 months), kyphosis, and fifth finger clinodactyly. The 49 XXXXY karyotype was confirmed twice.

Hormonal assays (LH, FSH, and testosterone) are usually within normal limits at this age [7,8]. In our patient, the testosterone level was low with a

TABLE 1. Phenotypic features.

Features	Cited frequency	Present case
Mental retardation	100%	+
Relative low birth weight	95%	+
Upward slanting palpebral fissures	75%	+
Epicanthal folds	80%	+
Strabismus	57%	-
Hypertelorism	87%	+
Malformed ears	73%	-
Broad nasal bridge	86%	+
Short neck	70%	+
Prognathism	50%	-
Short stature		+
Genital anomalies		
Hypoplastic scrotum	70-80%	+
Cryptorchidism	30%	+
Small penis	85%	+
Small testicles	80%	+
Decreased or female distribution of pubic hair	40%	-
Limited elbow pronation		+
Increased frequency of digital arch		-

TABLE 2. Skeletal abnormalities.

Abnormalities	Cited frequency	Present case
Radioulnar synostosis	70%	+
Abnormal ossification centers in hands		+
Fifth finger clinodactyly		+
Elongated radius		-
Pseudoepiphyses in hands and feet		-
Kyphosis		+
Scoliosis		-
Coxa valga		-

high FSH level and normal LH reading—results confirmed by HCG/LHRH challenge. Testicular biopsy was not performed. In fact, the classic lesion of dysgenesis and hyalinization of the seminiferous tubules is progressive following the supposed normal age of puberty.

The recurrent chest infections which occurred in our patient starting at six months of age can be explained by the IgA deficiency and possible IgG subclass deficiency, and the known increased inci-

dence of pulmonary disease in Klinefelter's syndrome, which, however, is a later phenomenon.

Treatment in our patient will consist of replacement therapy with long-acting testosterone, at age 11 to 12 years or older, and plastic surgery to correct the hypospadias. The overall prognosis in our patient, considering the mental retardation and infertility, is poor.

References

1. Smith WD. Recognisable pattern of human malformation, ed 3. Philadelphia: Saunders, 1982;64-66.
2. Kaplan SA. Clinical pediatric and adolescent endocrinology. Philadelphia: Saunders, 1982.
3. Caldwell PD, Smith DW. The XXY (Klinefelter's) syndrome in childhood: detection and treatment. *J Pediatr* 1972;80:250.
4. Fraccaro M, Kaigser K, Linesten J. A child with 49 chromosomes. *Lancet* 1960;2:899.
5. Zelesti WA, Houston CS, Pozsonyi J, Ying KL. The XXXXY chromosome anomaly report of three new cases and review of thirty cases from the literature. *Can Med Assoc J* 1966;94:1143.
6. Paulsen CA, Gordon DL, Carpenter RW, et al. Klinefelter's syndrome and its variants: a hormonal and chromosome study. *Recent Prog Horm Res* 1968;24:321.
7. Salbenblatt JA, Bender BG, Puck MH, et al. Pituitary-gonadal function in Klinefelter syndrome before and during puberty. *Pediatr Res* 1985;19:82.
8. Boudailliez B, Chanssain JL, Garnier PZ, et al. Le syndrome de Klinefelter chez l' enfant et a l' age de la puberte: exploration endocrinienne. *Ann Pediatr (Paris)* 1981;28:195.

Letters to the Editor

The *Annals of Saudi Medicine* welcomes letters to the Editor from its readers. They may be on any topic, though the Editor especially encourages discussion of papers published in the *Annals*. Letters should be no more than 100 typewritten lines in length, typed double-spaced, and submitted in triplicate. Letters may include one figure or brief table and up to five references. Submission of a letter constitutes permission for the *Annals* to use it for publication, letters should not duplicate similar material being submitted or published elsewhere, and the *Annals* reserves the right to edit letters submitted. Letters referring to a recent *Annals* article should be received within 6 weeks of the article's publication.

Lower-Lung-Field Tuberculosis in Saudi Arabia

To the Editor: Pandya et al [1] recently published a report on pulmonary tuberculosis in Saudi Arabia, but their report does not specify in detail the age of the patients. As a pediatrician, I am interested in knowing whether they encountered in their series any pediatric patients suffering from pulmonary tuberculosis, either primary or post primary. Childhood tuberculosis is the index of adult tuberculosis, but the disease is rare in the southern part of Saudi Arabia among the pediatric age group.

Although the rarity of the disease can be explained on the basis that most children are vaccinated against tuberculosis and the socioeconomic status of the people is high [2,3], a small number of patients we see from a rural area like Tihama have not been vaccinated and are undernourished. Some have a positive history of tuberculosis in the family, though they may be free of tuberculosis. It is known that vaccination against tuberculosis does not ensure 100% protection [4].

I would like to know the authors' comments on this matter.

Ghulam Nabi, MD
Department of Pediatrics
Civil Hospital

P.O. Box 737
Khamis Mushait, Saudi Arabia

References

1. Pandya L, Al-Sharif N, Maraey A, Madani A. Lower-lung-field tuberculosis in Saudi Arabia. *Ann Saudi Med* 1990;10(4):374-7.
2. Shanks NJ. B.C.G vaccine. *Saudi Med J* 1983;4(3):181-4.
3. Azad Chowdhury MAK. Infant feeding practices and immunization in the Khamis Mushait area. *Ann Saudi Med* 1989;9(1):19-22.
4. Chavalittamrong B, Chearskul S, Tuchinda M. Protective value of B.C.G. vaccination in children in Bangkok, Thailand. *Paediatr Pulmonol* 1986;2(4):202-5.

Reply

To The Editor: I thank Dr. Nabi for his comments. My comments in reply are as follows: We see only adult pulmonary tubercular patients, and the youngest patient in our series was 15 years old. Regarding the low prevalence of tuberculosis in Saudi children in the Southern region, all the adverse predisposing factors like low socioeconomic conditions, not receiving BCG protection, malnutrition, and positive family contact need study. We cannot really comment on this. A low prevalence of tubercular infection in normal children from the Northern region of Saudi Arabia has been shown by Hajjaj et al [1] in a small survey. In their study in children 5 to 14 years old who had not received BCG vaccination, only 4% showed tuberculin positivity, compared with 58% positivity in the age group 45 to 64 years. This indicates a pool of infected population who can develop active pulmonary tuberculosis. Most of them must have acquired tuberculosis during childhood. The low percentage of tuberculosis in children is due to changes in the socioeconomic structure.

Lalit Pandya, MD, MRCP
Sahary Chest Hospital
P.O. Box 7966
Riyadh 11472, Saudi Arabia

Reference

1. Al-Hajjaj M, El-Kassimi F, Abdullah A, Al-Orainey I. Prevalence of tuberculosis infection in the Northern Region of Saudi Arabia (abstract). In: Proceedings of the Conference on Lung Health, Boston, Massachusetts, A801.

The Prevalence of Brucellosis Among Veterinarians in Jordan

To the Editor: Brucellosis is a direct anthroponosis and has adverse effects on animal health and production. Although the disease affects a wide range of farm animals [1], in Jordan the disease is most common among goats and sheep. We investigated the prevalence of brucellosis among veterinarians in Jordan.

The study group consisted of a random sample of 66 veterinarians practicing in the different geographical areas of Jordan (33.84% of practicing veterinarians in Jordan) during the summer months of June through September 1986. These included general practitioners, administrators, and those working in diagnostic laboratories and abattoirs. A control group of 66 healthy subjects was picked randomly from a group of veterinarians possessing characteristics similar to the study group (i.e., age, sex, rural/urban background, consumption of dairy products) and the occupational contact with animals was also similar. Data were collected by two methods.

The first consisted of a specially designed questionnaire that was completed by each veterinarian. The information obtained included the age of the study participants, the type of animals handled, the geographical areas where they practiced, and the number of years they were in practice in Jordan. It also revealed the presence of the major symptoms of brucellosis, mainly recurrent fever, excessive sweating, back and joint pains, and weakness.

The second method consisted of serological evaluation. Blood samples were collected and the sera separated and examined serologically for brucellosis. The rose bengal test, tube agglutination test, and mercaptoethanol test were used according to the method of Alton et al [2]. Those examined who were seropositive with titers of 1:80 (134 IU/ml) or more in the tube agglutination test and confirmed positive by the mercaptoethanol test were considered subclinically infected. Those who also suffered at least two major brucellosis symptoms were considered clinically infected, put under medical supervision, and re-examined serologically after periods of between 2 to 3 weeks. Fisher's exact test was used

to test the significance between proportions, where $P < 0.05$ was considered significant.

Table 1 summarizes the results of this study. Of the veterinarians examined, 10.60% were clinically infected with brucellosis and placed under medical supervision, while a higher percentage (43.94%) were infected subclinically. The highest infection rate was among general practitioners (13.33%), especially those practicing in North Jordan (20%). Veterinarians practicing for less than 10 years (and aged from 31 to 40 years) suffered more clinical infections (6 of 42; 14.29%) and fewer subclinical infections (35.71%), when compared with those in practice for periods of 10 years or more (1 of 24; 1.4%, and 58.33%, respectively). Those veterinarians who showed clinical infection and underwent serological re-examination had a variety of increasing titers which declined over time with treatment.

In the control group of healthy subjects, there was one seropositive subject with no apparent symptoms who lived in the Amman urban area and was 42 years old.

Between 1973 and 1986, increasing cases of brucellosis of sheep and goats have been reported in isolated foci in Jordan [3]. In humans, the disease was rarely diagnosed between the years 1978 to 1983, but escalated during 1984 to 1986 [4].

In this work, however, the clinical infection was mainly due to contact with sheep and goats during *dystokia*, though in two cases accidental injection with live vaccine was considered the cause. Strain Rev. 1 was adopted for use by the Ministry of Agriculture for control of the disease in sheep and goats in Jordan, but the risk from personal accidental injection with the vaccine endangers the effectiveness of this main control measure against the disease. Young veterinarians practicing for less than 10 years are more exposed to infections, as the majority of them are working in direct contact with animals, whereas senior veterinarians with more than 10 years' experience may have developed resistance to the infection or work in offices as administrators and are therefore removed from exposure. The known serological cross reactivity between *Brucella* sp and other infections may influence the rate of subclinical infection reported in this work. The high clinical brucellosis infection rate indicates that the influence is negligible.

TABLE 1. The number and percentage of veterinarians in different areas of veterinary field showing clinical and subclinical brucellosis.

	Clinics	Laboratories	Abattoirs	Administration	Total
No. (examined)	45	12	6	3	66
Infection No. (%)					
Clinical	6(13.3) ^a	1(8.3)	0 ^b	0(00.0) ^b	7(10.6)
Subclinical ^c	19(42.2)	3(25.2)	4(66.7)	3(100) ^b	29(43.9)
Total positive	25(55.6)	4(33.3)	4(66.7)	3(100) ^b	36(54.5)

^aSignificant ($P < 0.01$) as compared with other areas of veterinary fields.

^bPercentage not meaningful because of the low number of veterinarians examined.

^cSeropositive cases with no current characteristic brucellosis symptoms.

Seropositive subjects who are currently asymptomatic may have been ill from previous exposure to *Brucella* or recent subclinical infection. All veterinarians have lived for at least 5 years outside of Jordan during the time of their veterinary training, a factor that may influence the high subclinical infection rate.

The results emphasize that the disease poses an occupational hazard among veterinarians in Jordan, and also indicate that contact with infected sheep and goats during labor and abortion is the main mode of transmission of the disease in Jordan. This contrasts with consumption of contaminated dairy products and other modes of transmission of the disease observed elsewhere in the world. In addition, it indicates the high prevalence of the disease among sheep and goats in Jordan.

An account of the veterinarians infected with brucellosis could be used as a means of locating cases of human brucellosis [5]. The current work indicates the existence of brucellosis as a public health and veterinary problem in Jordan, and urges the need for vigorous control measures.

Mahmoud N. Abo-Shehadeh, PhD

Attalah Z. Rabi, PhD

Nizar Abuharfeil, PhD

Department of Veterinary Medicine &
Animal Production

Department of Allied Health Sciences
Jordan University of Science and Technology
Irbid, Jordan

Acknowledgments

I would like to express my gratitude to my colleagues for their encouragement and cooperation.

References

1. Alton GG, Jones LM, Pietz DE. Laboratory technique in brucellosis, ed 2. FAO/WHO Publication 1970;79-112.
2. Ministry of Agriculture. The Hashemite Kingdom of Jordan. Annual Reports. 1971-86.
3. Ministry of Health, The Hashemite Kingdom of Jordan. Annual Reports. 1973-86.
4. Blood DC, Radostits OM, Henderson JA. Veterinary medicine. A textbook of the disease of cattle, sheep, pigs, goats and horses, ed 6. London: Bailliere Tindall, 1983;605-22.
5. Venkatakrishna-Bhatt H, Parikh JR, Nigam SK. Veterinarians and their distribution as a means to locate human brucellosis. Asian Med J 1985;28:641-50.

Measurement of Immunoglobulins G, M, and A in Idiopathic Osteoarthritis: A Suggested Explanation for Their Production

To the Editor: Measurement of serum immunoglobulins A, G, and M among 140 patients with primary idiopathic localized osteoarthritis of the knees has shown an increase of immunoglobulin A content in 111 cases (79%), immunoglobulin M in 106 cases (75%), and immunoglobulin G in 68 cases (48%). Our results will be discussed in the context of some of the most accepted theories that address the initiation and perpetuation of osteoarthritis.

Trauma has always been regarded as an important factor in the pathogenesis of osteoarthritis. In a previous work, the author suggested that repetitive trauma causes stiffening of the subchondral bone, resulting in increased wear of the overlying cartilage [1]. Other studies have shown that a subfracture level of trauma can accelerate

remodeling in the zone of calcified cartilage with reduplication of the tidemark which could result in thinning of the noncalcified zone [2]. However, it seems that trauma alone cannot cause inflammation in joints after a period of time and that there must be a perpetuating factor for the production of osteoarthritis. It has also been stated that osteoarthritic synovium secrete immunoglobulins more than do tissues from normal controls and that these immunoglobulins are further trapped in the cartilage-forming immune complexes, which may be a common feature of the disease [3].

One hundred forty cases of idiopathic localized osteoarthritis of the knees were carefully chosen for the study. Urine and stool analysis were done in all cases to exclude the possible presence of parasitic infestations. No other rheumatic diseases could be detected in these patients. They comprised 99 females and 41 males, and their age ranged from 40 to 75 years (mean, 54.3).

One hundred age-matched control cases were included for comparison of data. All these subjects were free of parasitic infestations, never complained of knee problems, and did not have any other subset of osteoarthritis. They comprised 59 females and 41 males. Their age ranged from 40 to 75 years (mean, 54.3).

Immunodiffusion plates (Hoechst) were used. The nor-partigen part was used for the measurement, which was rendered in milligrams per deciliter.

The levels of immunoglobulins G, M, and A proved to be significantly higher than those of the control group. The results are shown in Table 1, together with the statistical analysis. No statistically significant difference was found between the ages of both groups (Table 1).

The results of our study could be explained by two previously described hypotheses. One is that inflamed synovium secrete immunoglobulins more than do tissues from normal subjects [3]; however, the locked immunoglobulins cannot efflux back to the circulation unless the interstitial hyaluronate-protein complexes are fragmented by enzymes associated with the inflammatory process. Because it is assumed that the production of hyaluronic acid from osteoarthritic joints is very poor, the route for immunoglobulins to pass into the circulation will always be present in a previously inflamed joint that has passed to chronicity [4].

TABLE 1. Serum immunoglobulins G, M, and A in both knee osteoarthritis patients and controls.^a

Subjects	Age (yr)	IgG	IgM	IgA
Control (N = 100)	49.2 ± 20.2	1280 ± 211	151 ± 32	209 ± 46
Osteoarthritis patients (N = 140)	54.3 ± 19.6	1872 ± 444	206 ± 54	315 ± 96
<i>t</i>	1.96	12.36	9.1	11.32
<i>P</i>	> 0.05	> 0.0001	> 0.0001	> 0.0001

^aAll values are given as the mean ± SD.

One of the most provocative theories relating to the cause of idiopathic osteoarthritis is that the aneural and avascular state of articular cartilage isolates its matrix components from the immune recognition system, with the possibility that some of the matrix proteins are not recognized by the immune system as autogenous. When they escape from the cartilage into the synovial fluid, the local macrophages and lymphocytic elements view them as antigens [5].

This theory provides a hypothetical explanation for the means by which even a minor injury to the cartilage may serve as the initiating event in a local autoimmune causation or perpetuation mechanism which over time becomes sufficiently severe to destroy parts of the cartilage by humoral or cellular cytotoxic antibody responses. The result of our work might be regarded as the humoral response of that theory and is in accordance with it.

Mohamed Bassiouni, MD, PhD

Hassan Bassiouni, MD

Mostapha El-Dahan, MSc

Department of Rheumatology and
Rehabilitation

Al-Azhar University

Cairo, Egypt

References

1. Rodin EL. Mechanical factors in the etiology of osteoarthritis. In: Pyron JG (ed). *Epidemiology of osteoarthritis*. Paris: Ciba-Geigy, 1981;136-9.
2. Oegema TR Jr, Hofmeister F, Carpenter RJ, et al. Acceleration of calcification in the zone of calcified cartilage in rabbits. *Trans Orthop Res Soc* 1988;13:512.
3. Loyau GC. Osteoarthritis: current trends and future prospects. *Eular Bull J Educ Inform Rheumatology* 1987;16(No. 4).
4. Nettelbladt E, Sundblad L, Jonsson E. Permeability of

the synovial membrane to proteins. *Acta Rheumatol Scand* 1963;9:28.

5. Cooke TD. Immune pathology in polyarticular osteoarthritis. *Clin Orthop* 1986;213:41.

Warfarin Embryopathy and Heart Disease

To the Editor: It has been known for years that the use of warfarin during pregnancy can cause fetal malformations. Recently a child was born at our hospital with characteristics similar to those reported previously [1-3].

A 1790-gm male infant was born at 33 weeks' gestation to a 20-year-old gravida 1, para 0, abortus 0 female. She had had mitral valve replacement (St. Jude's prosthetic #33) for severe pulmonary hypertension at the age of 14 and was treated postoperatively with warfarin. She continued to use 6 to 7.5 mg of warfarin daily throughout her pregnancy with no untoward side effects. Other medications taken during pregnancy were iron and multivitamins.

At birth, the infant's condition was good and he required no resuscitation. Apgar scores were 8 and 9 at one and five minutes. The infant was moderately hypotonic, pale, and had intermittent cyanosis with mild respiratory distress. His head circumference was 30 cm. The infant was small for dates. His face was broad with a hypoplastic midportion and there was a markedly depressed nasal bridge and hypoplastic alae nasi (Figure 1). Systemic examination findings including the fundi were normal. The services of a clinical geneticist were not available. A right parietal cephalohematoma appeared on day 2. Cyanosis abated after the infant was placed in oxygen (FiO₂ 30%). After initial nasogastric tube feeding, he was able to feed by bottle beginning at 27 days of life and was discharged at 60 days, weighing 3020 gm.

The results of laboratory data included hemoglobin, 197 gm/L; hematocrit, 58.1%; and white blood cell count, 11,600/mm³. Clotting studies at birth showed prothrombin time (PT), 19.6 (control, 13) and at age 15 days, PT, 12 (control, 12.5) and partial thromboplastin time, 35.5 (control 39.7). Ultrasound studies of the brain, kidney, and spleen were normal. Skeletal survey included roentgenograms of the long bones which were



FIGURE 1. Photograph of the infant, showing depressed nasal bridge and alae nasi.

normal, but x-ray study of the abdomen showed stippling of the sacral vertebrae.

At 4 months of age (corrected, 2 months and 1 week), he was still below the 10th centile for weight and height. He was able to hold up his head and smile. His nasal deformity did not change, and except for occasional nasal obstruction, he remained well.

Warfarin is a potent teratogen, known since 1966, and this case lends further support to this view. The teratogenic effect of warfarin may result from its chemical structure, or may be due to bleeding into the developing cartilages. The precise mechanism of its action is unknown but the effect appears to be dose dependent [1,2].

The consistent features described in the literature in 11 infants are similar to those in the present patient, and consist of nasal hypoplasia and stippled epiphyses. Other abnormalities reported include optic atrophy, cataract, microcephaly, mental retardation, cranial nerve palsies, hydro-

cephalus, flexion contracture, and asplenia [1-3].

A large number of pregnancies occur following valve replacement in the third world, where advice against pregnancy may not be accepted for various social reasons. A variety of treatment regimens have been devised in an effort to minimize the risk to both mother and fetus, including subcutaneous heparin and dipyridamole, high-dose subcutaneous heparin, and long-term intravenous heparin [2,4]. The critical period for warfarin embryopathy is the first 6 to 9 weeks of gestation [1]. When the use of warfarin during pregnancy is essential, the teratogenic risk, though small, should be discussed with the patient. The infant should be carefully examined for possible teratogenetic effects, as all the features of warfarin embryopathy may not be present in a given case.

Sudhakar B. Patil, MBBS, MRCPI, DCH

Department of Pediatrics

King Faisal Military Hospital

P.O. Box 101

Khamis Mushayat, Saudi Arabia

References

1. Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980;68:122-40.
2. DeSwiet M. Anticoagulants. *Br Med J* 1987;294:428-30.
3. Stevenson RE, Burton M, Ferlauto GJ, Taylor HA. Hazards of oral anticoagulants during pregnancy. *JAMA* 1980;243(15):1549-51.
4. Iturbe-Alessio I, Fonseca M, Mutchinik O, et al. Risk of anticoagulant therapy in pregnant women with artificial heart valves. *N Engl J Med* 1986;315:1390-3.

Trichotillomania

To the Editor: Recently, trichotillomania has been classified under the disorders of impulse control and defined in a discrete and comprehensive way [1,2]. Trichotillomania is a chronic maladaptive and self-destructive pattern of behavior with a neurotic dimension and results in considerable cosmetic impairment, social isolation, and other dangerous complications [3]. For some it is a symbolic dermatological expression of underlying psychosocial stresses which are often denied by patients [4,5]. Although the sociodemographic correlates of trichotillomania continue to be

explored, it is known to have a predilection for female subjects and is predominantly found in children, as has been substantiated by an experimental study [6] and also strongly supported by the observations of others [1,4,5]. Further, there is a general agreement that trichotillomania is a heterogeneous disorder, and therefore a variety of etiological interpretations have been proposed by various researchers [7-9]. There is, however, a dearth of research on the biological aspects of the disorder.

It is evident from reports in the literature that trichotillomania can coexist with trichophagy [10], thumb sucking [11], bulimia [12], atypical depression [13], psychosomatic disorders [14], obsessional neurosis [15] and other mental disorders [1]. Interestingly, according to DSM-III-R criteria, substance abuse disorders contribute to the development of trichotillomania. The presentation of trichotillomania is characteristic, but it can be confused with many different types of alopecia, as reported by various researchers [4,15]. In relation to this, punch biopsy of affected scalp is useful in confirming the clinical diagnosis of trichotillomania [1,4]. Numerous therapeutic modalities have been derived from the theoretical concepts of trichotillomania, and these range from behavioral techniques [16-21] to psychodynamic therapies [4,12,22] to psychotropic drugs [3,13]. Though a matter of individual preference, the best approach for the treatment of trichotillomania would be a combination of pharmacological drugs, especially clomipramine, and one of the behavioral techniques.

We describe a case of trichotillomania, knuckle biting, and nocturnal enuresis which occurred consecutively in the same patient.

A 19-year-old unmarried male Palestinian medical student, living in Yemen, was brought by his parents to the Psychiatric Clinic of Buraidah Mental Health Hospital because for the previous two years he had been pulling out his hair. The solitary act of pulling out hair, preferably from the left temporoparietal region of the scalp using exclusively the left hand, was always preceded by emotional tension caused by constant parental pressure concerning his studies, outdoor activities, and other relatively unimportant matters. Following each episode of hair pulling, the patient would feel relief and hide the evulsed hairs under the ta-

blecloth or bed, rather than eating them. This chronic self-inflicted behavior resulted in incomplete loss of hair and his educational standing also decreased. Other than the hair pulling, the patient did not exhibit any manifestations of psychiatric illness. Retrospective evaluation of the patient revealed that early developmental milestones were not delayed, except nocturnal bedwetting which persisted until adolescence. Closely following this, the patient began to exhibit repeated self-mutilating behavior, most often evoked by angry spells, characterized by biting the knuckles of the second, third, fourth, and fifth metacarpophalangeal joints of only the right hand. This resulted in depigmentation of the dermis punctuated by pinpoint hemorrhages. Ultimately both the nocturnal enuresis and knuckle biting spontaneously remitted at age 14 and 17, respectively.

Though the family history revealed no overt neuropsychiatric illness, the father appeared to be a rigid and strict disciplinarian and the mother showed neurotic tendencies. The milieu in Palestine and Saudi Arabia described by the parents and patient included a variety of adverse psychosocial problems that affected the entire family.

At physical examination the patient had a number of circumscribed areas of relative hair loss, more marked on the left side of the scalp. Besides small broken hairs, long ones were also visible. There were no signs of inflammation on the affected areas of the scalp. Moreover, both the dermatologist and pediatrician ruled out clinically the organic nature of incomplete alopecia of the scalp. Further systemic examination and laboratory tests were negative. Regarding the mental status evaluation, the patient did not exhibit anxiety, depression, obsessive neurosis, or psychosis.

We describe a case of adult trichotillomania characterized by a recurrent irresistible urge for the patient to pull out his own hair, supported by other salient features. Adult trichotillomania is a relatively uncommon disorder. It would be extremely relevant to differentiate childhood trichotillomania from the adult type. The adult type is strongly linked with psychotic behavior and has different sociodemographic and etiopathological correlates, including treatment strategies [1,8,15]. In our patient the affected area was the

scalp and this is the most common area reported by others [1,23,24]. However, in our patient the temporoparietal region was affected, as opposed to the crown and occipital areas of the scalp, and this is an atypical finding. It has been reported in the literature [3,4,10,25], and was also evident in our case, that most patients with trichotillomania pull their hair out during solitude, a simple protection against embarrassment and shamefulness, and hide the evulsed hairs rather than eating them. What is most intriguing about our patient was that the trichotillomania was followed by knuckle biting, which probably served as a tension-reducing behavior. This has not been reported previously in the psychiatric literature. The knuckle biting could have been considered finger biting, but we felt the need to term the behavior as knuckle biting, since it specifically and restrictively involved only the knuckles. Although the knuckle biting was not associated with any other neurotic habits, as had been reported in cases of nail biting [26], it in some respects appeared identical to the latter behavior. Another interesting phenomenon was that knuckle biting was preceded by nocturnal enuresis, which indicated early on a disturbed interpersonal family relationship and a highly strung, maladjusted patient.

Trichotillomania has been viewed as a multifaceted disorder, and therefore numerous explanations have been advanced for understanding the nature of the behavior [7-9,14,27-29]. With regard to the present case, it is, however, noteworthy that the consecutive occurrence of the triad of psychological disorders might be attributed to the persistent frustrations arising from multiple lifelong stressful situations, not only originating in the family but also from society at large.

A variety of therapeutic modalities have been recommended for the treatment of trichotillomania [3,4,12-22,30]. However, during his short stay, the patient was trained to use competence response therapy by clenching his fist for three minutes when he developed or felt likely to develop the urge to pull out his hair. Further, besides parental counseling, this technique was coupled with monetary rewards and a couple of brief psychotherapeutic sessions which resulted in a fairly good response.

Nassem Akhtar Qureshi, MD, MBBS
T. K. Gowrishanker, MBBS, MD, DPM
 Mental Health Hospital
 P.O. Box 2292
 Buraida, Saudi Arabia

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, ed 3, revised. Washington, DC: American Psychiatric Association, 1987.
2. World Health Organization. Mental disorders, glossary, and guide to their classification in accordance with the tenth revision of international classification of diseases. Geneva: World Health Organization.
3. Swedo SE, Leonard HL, Rapoport JL, et al. A double blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). *N Engl J Med* 1989;321(8):497-501.
4. Muller SA. Trichotillomania. *Dermatol Clin* 1987;5(3):595-601.
5. Gupta MA, Gupta AK, Haberman HF. The self-inflicted dermatoses, a critical review. *Gen Hosp Psychiatry* 1987;9(1):45-52.
6. Reinhardt V, Reinhardt A, Houser D. Hair pulling and eating in captive rhesus monkey troops. *Folia Primatol (Basel)* 1986;47(2-3):158-64.
7. Galski T. Hair pulling (trichotillomania). *Psychoanal Rev* 1983;70(3):331-46.
8. Oranje AP, Peereboom-Wynia JD, De Raeymaecker DM. Trichotillomania in childhood. *J Am Acad Dermatol* 1986;15(4 pt 1):614-9.
9. Gelder M, Gath D, Mayou R. Psychiatry and medicine—skin disorders. In: *Oxford Textbook of Psychiatry*. New York, London, Oxford University Press, 1983;384.
10. Tamminen J, Rosenfeld D. CT diagnosis of a gastric trichobezoar. *Comput Med Imaging Graph* 1988;12(6):339-41.
11. Knell SM, Moore DJ. Childhood trichotillomania treated indirectly by punishing thumb sucking. *J Behav Ther Exp Psychiatry* 1988;19(4):305-10.
12. Hall JR, McGill JC. Hypnobeavioral treatment of self-destructive behavior: trichotillomania and bulimia in the same patient. *Am J Clin Hypn* 1986;29(1):39-46.
13. Krishnan RR, Davidson J, Miller R. MAO inhibitor therapy in trichotillomania associated with depression: case report. *J Clin Psychiatry* 1984;45(6):267-8.
14. Meyer AE, Haag A. Psychosomatics of trichotillomania and related states or disorders. *Psychother Psychosom* 1984;42(1-4):119-23.
15. Krishnan KR, Davidson JR, Guajardo C. Trichotillomania—a review. *Compr Psychiatry* 1985;26(2):123-8.
16. De Luca RV, Holborn SW. A comparison of relaxation training and competing response training to eliminate hair pulling and nail biting. *J Behav Ther Exp Psychiatry* 1984;15(1):67-70.
17. Tarnowski KJ, Rosen LA, McGrath ML, Drabman RS. A modified habit reversal procedure in a recalcitrant case of trichotillomania. *J Behav Ther Exp Psychiatry* 1987;18(2):1157-63.
18. Lutzker JR, Lamazor EA. Behavioral pediatrics: research, treatment, recommendations. *Prog Behav Modif* 1985;19:217-53.
19. Deshpande SN, Mehta M. Aversion therapy in the treatment of trichotillomania. *J Pers Clin Studies* 1989;5(2):242-4.
20. Dahlquist LM, Kalfus GR. A novel approach to assessment in the treatment of childhood trichotillomania. *J Behav Ther Exp Psychiatry* 1984;15(1):47-50.
21. Mathew A, Kumaraiah V. Behavioral intervention in the treatment of trichotillomania. *Indian J Paediatr* 1988;55(3):451-3.
22. Barabasz M. Trichotillomania—a new treatment. *Int J Clin Exp Hypn* 1987;35(3):146-54.
23. Schnurr RG. Psychological assessment and discussion of female adolescents with trichotillomania. *Adolesc Psychiatry* 1988;15:463-70.
24. Singhal PK, Bhatia MS, Dhar NK, Nigam VR. Trichotillomania. *Indian Paediatr* 1988;25(3):290-2.
25. Lamerton AJ. Trichobezoar: two case reports—a new physical sign. *Am J Gastroenterol* 1984;79(5):354-6.
26. Klackenberg G. A prospective longitudinal study of children: data on psychic health and development up to 8 years of age. *Acta Paediatr Scand* 1971;239:224.
27. Bekhor PS. Common hair disorders. *Aust Fam Physician* 1986;15(7):868-74.
28. Cossidente A, Sarti MG. Psychiatric syndromes with dermatologic expression. *Clin Dermatol* 1984;2(4):201-20.
29. Aldridge RD. Hair loss. *Br Med J* 1984;289(6450):985-9.
30. Stevens MJ. Behavioral treatment of trichotillomania. *Psychol Rep* 1984;55(3):987-90.

Announcements

The *Annals of Saudi Medicine* is pleased to publish announcements of educational opportunities of interest to its readers. For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least 6 months before the date of occurrence. Please send relevant information to the *Annals of Saudi Medicine*, Publications Office, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

King Saud University Fellowship in Pathology

King Saud University announces the inception of a 5-year joint fellowship training program in pathology. The training will be at King Khalid University Hospital, King Faisal Specialist Hospital and Research Centre, and Riyadh Armed Forces Hospital, and is a full-time program. Application is open to interested and suitably qualified residents from all over the Kingdom. To be eligible, applicants will meet the following criteria:

1. Doctors who hold MB,BS from King Saud University or equivalent degree with at least Good grade.
2. Doctors who have finished their internship in a recognized hospital with at least a Very Good grade.
3. Successful completion of a selection examination and personal interview.
4. Applicants from other institutions should submit a letter from his/her employer that he/she will be sponsored during the whole period of training.

Applications and inquiries should be sent to the Director, Postgraduate Medical Education, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Radiopharmaceuticals from King Faisal Specialist Hospital and Research Centre

King Faisal Specialist Hospital and Research Centre manufactures various radiopharmaceuticals at its Radionuclide and Cyclotron Operations facility with the aid of model CS-30 Cyclotron. These radiopharmaceuticals are produced according to international standards of good manufacturing practice. The Research Centre meets the high standards of quality assurance and environmental safety with regard to radiopharmaceuticals.

Radiopharmaceuticals currently produced and available for distribution throughout the Kingdom and to adjoining Arab states are as follows: thallous (Tl-201) chloride injection ($T_{1/2} = 73$ h); gallium (Ga-67) citrate injection ($T_{1/2} = 78.3$ h); iodine-123 capsules ($T_{1/2} = 13.1$ h); iodine-123 oral solution ($T_{1/2} = 13.1$ h); iodine-123 orthoiodohippurate solution ($T_{1/2} = 13.1$ h); rubidium (Rb-81) $\rightarrow$ krypton (Kr-81 m) generator ($T_{1/2} = 4.58$ h - 13 s); indium (In-111) oxine ($T_{1/2} = 67.92$ h) for cell labeling; indium (In-111) DTPA for cisternography ($T_{1/2} = 67.92$ h).

Suggestions from the medical community for additional cyclotron-produced needs are welcome.

Inquiries concerning the availability, price schedule, and technical information on specific radiopharmaceuticals should be directed to: Abbass H. Al-Marzouky, MD, Executive Director, Research Centre, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia (Fax No. 966-1-441-4839).

Joint Board for Postgraduate Medical Education Symposia for 1411

The Joint Board for Postgraduate Education is pleased to announce the following symposia for 1411.

1. Postgraduate and Continuing Medical Education; College of Medicine, King Saud University, 21-22 Shawwal 1411 (5-6 May 1991).

For further information, contact the Joint Board Office, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia; telephone (01) 467-1556 or 1564; telefax 481-1853; telex 403748 DARAYAH SJ.

King Faisal Specialist Hospital and Research Centre: Educational Activities

King Faisal Specialist Hospital and Research Centre is pleased to announce the following educational activities for 1411.

1. FMGEMS Examination; 12-13 Muharram 1412 (23-24 July 1991)

For further information, contact Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211; telephone 464-7272, extension 1865 or 1834, fax 442-7237.

Fellowship and Diploma Programs, College of Medicine, King Saud University

The Postgraduate Centre for Medical Education, College of Medicine, King Saud University, announces the schedule of new intakes for the following diploma and fellowship programs for the year 1412:

Diploma in Dermatology: Selection examination (written): 7 Rabi Al Awal 1412 (15 September 1991); interview: 10 Rabi Al Awal 1412 (18 September 1991); starting date of acceptance of applications: 16 Ramadan 1411 (1 April 1991); deadline for submission: 23 Muharram 1412 (3 August 1991).

Fellowship Programme in Anaesthesia: Selection examination and interview: 28 Safar 1412 (7 September 1991); starting date of acceptance of application: 16 Ramadan 1411 (1 April 1991); closing date: 16 Muharram 1412 (27 July 1991).

Application forms, list of requirements, and further information can be obtained from the Residency Training Programme Secretary, Postgraduate Centre, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, or please call 467-1551, 467-1556, or 467-1564.

INFORMATION FOR AUTHORS

THE EDITORS of the *Annals of Saudi Medicine* welcome contributions from our readers. The *Annals* will consider for publication manuscripts of interest to readers in Saudi Arabia, the Middle East, and around the world. All submissions are subject to review by the Editorial Board and by referees in appropriate specialties.

Submission of Manuscripts. Manuscripts are received with the understanding that they are not under simultaneous consideration by another publication. An abstract published prior to a full report is not regarded as a duplicate publication. The author's transmittal letter must accompany the manuscript and contain these statements: "The manuscript has been seen and approved by all authors involved and is neither being published nor being considered for publication elsewhere. The authors transfer copyright to the *Annals of Saudi Medicine*." Accepted manuscripts may not be published elsewhere without *Annals'* permission.

Manuscript Preparation. The format of the *Annals of Saudi Medicine* complies with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," published by the International Committee of Medical Journal Editors in Vancouver, British Columbia, in 1979 (the widely accepted "Vancouver style"), as described in the *Annals of Internal Medicine* (1982; 96 [pt 1]: 766-71). With the exception of blood pressure, all units of measurement and laboratory values must be expressed in SI units; conventional units may be included parenthetically. Authors are referred to *Annals of Internal Medicine* (1987; 106 [1]: 114-29) for guidance in the use of SI units. Manuscripts, including tables, references, and figure legends, must be typewritten, double-spaced, on 8 1/2 × 11 inch (21.5 × 28 cm) or size A4 paper, with margins of at least 1 inch (2.5 cm). Pages should be numbered consecutively, beginning with the title page and continuing through the last page of typewritten material. One original and two photocopies of the entire manuscript should be submitted, along with three sets of photographs.

Title Page. The title page must contain (1) title of the article, (2) correct names of each author plus highest academic degree for each, (3) each author's official academic and/or clinical title and affiliation, (4) name and address of the institution(s), (5) name and address of author to whom correspondence should be sent, if it differs from the first author, and (6) any disclaimers. For case reports, it is recommended that the number of authors be limited to four. Acknowledgment of support should be included in the Acknowledgment section at the end of the article.

Abstracts. All original articles must contain an abstract of not more than 200 words. The abstract should include statements of problem, method of study, results, and conclusions.

Manuscript Format. Most original articles have the following format: Introduction (the question the paper intends to answer); Materials and Methods (the study design and methods, definitions such as for diagnostic criteria, the population or patient samples, and laboratory and statistical methods); Results (the pertinent findings in a logical sequence with tables and figures as necessary); and Discussion (conclusions based on the findings, evidence from the literature that supports the conclusions, conflicting evidence, applicability of the conclusions, and implications for future research or clinical applications). Authors might consult recent issues of the *Annals* for examples of appropriate format.

References. List references, double-spaced, in consecutive numerical order (the order of citation in the manuscript, not alphabetically). Once a reference is cited, all subsequent citations should be to the original number. All references must be cited in the text or tables. Unpublished data and personal communications will not be accepted as references. References to journal articles should include in this order, (1) authors, (2) title, (3) journal name (as abbreviated in *Index Medicus*), (4) year, (5) volume and issue number, and (6) inclusive page numbers. References to books should include (1) authors, (2) chapter title (if any), (3) editors names (if any), (4) title of book, (5) city of publication, (6) publisher, and (7) year. Volume and edition numbers and specific page numbers should be included when appropriate. The author is responsible for the accuracy and completeness of the references and for their correct textual citation. Refer to reference citations and listings in the text for proper format.

Illustrations. Three copies of all figures or photographs should be included with the submitted manuscript. Photographs must be high-contrast, glossy, black and white prints, unmounted and untrimmed, with preferred size between 4 × 5 inches and 5 × 7 inches (10 × 13 cm and 13 × 18 cm). Color transparencies or photos will be accepted at the discretion of the Editorial Board. Figure number, name of senior author, and an arrow indicating "top" should be typed on a gummed label and affixed to the back of each illustration. Slides must be marked for "front" as well as "top." All lettering, arrows, or other artwork must be done by an artist or draftsman. Graphs and charts must also be prepared professionally by an artist or draftsman. Written permission must accompany any photograph in which the subject can be identified or any illustration that has been previously published. All illustrations ("figures") must be numbered as cited in the text in consecutive numeric order.

Legends. Captions for the figures must be typed, double-spaced, and must not appear on the figures. For photomicrographs, the legend should include the original magnification and stain used.

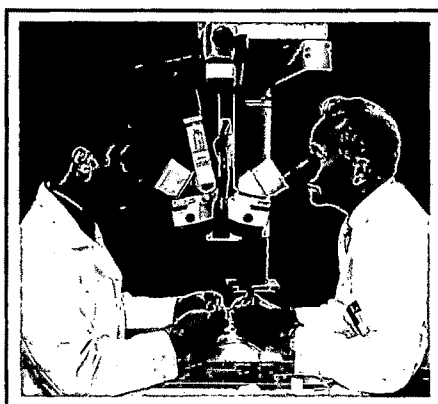
Tables. Each table should be typed double-spaced, including all headings. Verify tabular statistics to make sure they tally and match data cited in the text.

Responsibilities of Authors. The authors are entirely responsible for accuracy of all statements and data (including drug dosages) contained in the manuscript, accuracy of all reference information, and for obtaining and submitting permission from the author and publisher of any previously published material included in the submitted manuscript. The corresponding author will receive an edited manuscript for "final author approval." The author should review this carefully, as he is responsible for all changes in his work, including changes made by the copy editor.

Informed Consent. All manuscripts reporting the results of experimental investigation involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after approval of the experimental protocol by a local human ethics committee.

Submit manuscripts to the Publications Office, *Annals of Saudi Medicine*, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone: (01) 464-7272, extension 1817.

**KING FAISAL SPECIALIST HOSPITAL
AND
RESEARCH CENTRE**



Invites Applicants for the Following Fellowship Programs

Cardiovascular Diseases

Cardiology
Pediatric Cardiology
Thoracic Cardiovascular Surgery

Oncology

Hematology
Medical Oncology
Pediatric Hematology-Oncology

Medicine

Endocrinology
Gastroenterology
Infectious Diseases
Nephrology
Pulmonology and Critical Care
Rheumatology

Pediatrics

Allergy and Clinical Immunology
Neonatal/Perinatal Medicine
Gastroenterology and Hepatology
Genetics, Metabolic Diseases,
and Endocrinology
Infectious Diseases
Nephrology
Neurology

We are a major tertiary care center providing a unique environment to train subspecialists. There are patients with unusual clinical entities, highly qualified staff, state-of-the-art equipment, and a total commitment by Administration to train Saudi physicians to assume the role of subspecialists in the Kingdom of Saudi Arabia. Applicants must be Saudis who are Arab Board certified in their specialty (or equivalent certification).

Contact Person:

Dr. Abdullah Al-Dalaan, Deputy Director, Academic Affairs and Postgraduate Education
(MBC-36), King Faisal Specialist Hospital and Research Centre
P.O. Box 3354, Riyadh 11211, Saudi Arabia
Telephone: 464-7272 Ext. 1832 or Fax: 442-7237

المدونات الطبية السعودية

هيئة التحرير

رئيس التحرير الدكتور بيتري هيردسون

الدكتور عبدالعزيز المشاري
الدكتور منصور النزهة
الدكتور خالد طبارة
الدكتور سعدي طاهر
الدكتور نادر فريد

الدكتور محمد أخت
الدكتور ماجد عامر
الدكتور كارلوس دوران
الدكتور صلاح الفقيه
الدكتور محمد زهير القاوي

مساعدة التحرير:

فرجينيا جي كروزير
شيرلي موفيت

هيئة النشر:

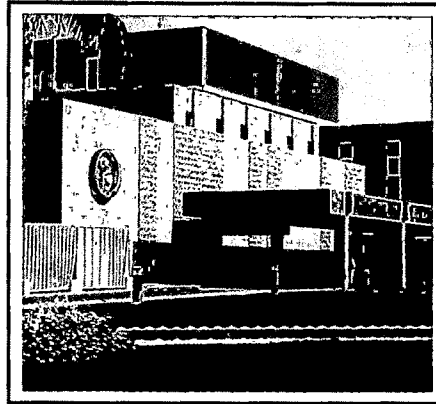
رئيس التحرير: الدكتور بيتري هيردسون
المحرر الإداري: الدكتور سعدي طاهر
محرر النصوص العربية: الدكتور محمد زهير القاوي
محرر فني: بيتي نتزون
مساعدة محرر فني: ماري آن دي سانتس

المدونات الطبية السعودية مجلة تنشر بموجب الأمر الملكي السامي رقم م/٥/٢٤٢٢٣ بتاريخ ١٤ شوال عام ١٤٠٠ هـ. وتصدر مرة كل شهرين، وهي مشروع مشترك بين كل من كلية الطب ومستشفى الملك خالد الجامعي - جامعة الملك سعود، صندوق بريد ٢٩٢٥ - الرياض ١١٤٦١، المملكة العربية السعودية، ومستشفى الملك فيصل التخصصي ومركز الأبحاث، صندوق بريد ٣٣٥٤ - الرياض ١١٢١١، المملكة العربية السعودية. يتم صف وطبع المجلة بمطابع جامعة الملك سعود. يتم توزيع المدونات بواسطة قسم البريد التابع لإدارة الخدمات الإدارية بمستشفى الملك فيصل التخصصي ومركز الأبحاث. كما يتولى قسم الترجمة في هذه الإدارة إعداد الملخصات العربية بالاشتراك مع الدكتور محمد زهير القاوي. كل المراسلات والاستفسارات وطرق الحصول على المستلزمات ترسل إلى مكتب المطبوعات على العنوان التالي:

مكتب المطبوعات
مدونات الطب السعودي
مستشفى الملك فيصل التخصصي ومركز الأبحاث
ص.ب. ٣٣٥٤
الرياض ١١٢١١ - المملكة العربية السعودية

الآراء التي ترد في المقالات المنشورة تعبر عن رأي أصحابها فقط ولا تعبر عن وجهة نظر مجلة المدونات الطبية السعودية. لا يسمح بإعادة طبع أي جزء من المجلة أو نسخه بأي شكل وبأي وسيلة سواء أكانت إلكترونية أو آلية، بها في ذلك التصوير والتسجيل أو الإدخال في أي نظام حفظ أو استعادة معلومات إلكتروني، بدون الحصول على موافقة مسبقة من إدارة المجلة.

**KING FAISAL SPECIALIST HOSPITAL
AND
RESEARCH CENTRE**



**Invites Applicants for the Following
Full-Time Postgraduate Training Programs**

Arab Board in Internal Medicine

Arab Board in Obstetrics and Gynecology

Arab Board in Pediatrics

Arab Board in Surgery

Qualifications:

1. Must be a Saudi national.
2. Must have obtained a grade of "Good" or higher in MBBs.
3. A letter of sponsorship is required if candidate is sponsored by another Institution.

Deadline for Application: 30 June, 1991

Contact Person:

Dr. Abdullah Al-Dalaan, A.B.I.M., Deputy Director
Academic Affairs and Postgraduate Education (MBC-36)
King Faisal Specialist Hospital and Research Centre
P.O. Box 3354, Riyadh 11211, Saudi Arabia
Telephone: 464-7272 Ext. 1832 or Fax: 442-7237

ANISTREPLASE

EMINASE

ANISOYLATED LYS-PLASMINOGEN STREPTOKINASE ACTIVATOR COMPLEX (APSAC)

PRESCRIBING INFORMATION



Presentation

EMINASE is supplied as a white to off-white sterile lyophilised powder in vials containing 30 Units of the p-anisoylated derivative of the primary (human) lys-plasminogen-streptokinase activator complex (APSAC; anistreplase) together with buffering and stabilising agents.

Indications

EMINASE is indicated in the treatment of acute myocardial infarction to establish reperfusion, preserve left ventricular function, limit infarct size and to reduce mortality.

Clinical studies have shown that EMINASE significantly reduces 30-day and 1-year mortality, limits infarct size and preserves left ventricular function.

Dosage and Administration

30 Units of EMINASE should be given as a single slow intravenous (IV) injection over 2-5 minutes. *Do not administer by intramuscular injection.*

EMINASE should be administered as soon as possible after the onset of symptoms of myocardial infarction.

See Package Insert Leaflet for details of preparation and administration.

Contra-Indications

Since thrombolytic therapy increases the risk of bleeding, EMINASE is contra-indicated in the following situations: 1. Surgery or major trauma within the previous 10 days. 2. Peptic ulceration, gastro-intestinal bleeding or other internal bleeding within the past 6 months. 3. Known bleeding diathesis. 4. History of cerebrovascular accident. 5. Severe, uncontrolled hypertension. 6. Known intracranial neoplasm or aneurysm. 7. Recent (within 2 months) neurosurgical procedure.

EMINASE should not be administered to patients who have experienced severe allergic reactions to this product or streptokinase.

Precautions and Warnings

Patients with any condition in which bleeding constitutes a significant hazard, or in which it would be particularly difficult to manage because of its location, should be monitored carefully. The risk associated with EMINASE therapy may be increased in such patients and should be weighed against the anticipated benefits.

Following administration of EMINASE, venepuncture and other invasive procedures should be kept to a minimum in order to reduce the risk of bleeding. In patients undergoing cardiac catheterisation, the catheter sheath should not be removed until 24 hours after dosing.

In the following conditions, the risks associated with thrombolytic therapy may be increased and should be weighed against the anticipated benefits: ● haemorrhagic diabetic retinopathy or other haemorrhagic conditions ● subacute bacterial endocarditis ● atrial or ventricular mural thrombosis, intracardiac tumours and aortic aneurysm ● septic thrombophlebitis or occluded AV cannula at a seriously infected site ● haemostatic defects including those secondary to severe hepatic or renal disease ● recent or current treatment with oral anticoagulants.

Hypotension, sometimes severe, has occasionally been observed soon after intravenous EMINASE administration. It is not recommended that EMINASE be administered rapidly (less than 2 minutes).

Re-administration

Because of the increased likelihood of resistance due to antistreptokinase antibody, EMINASE may not be effective if administered more than 5 days after prior EMINASE or streptokinase therapy, particularly between 5 days and 12 months. Furthermore, increased antistreptokinase antibodies after EMINASE or streptokinase may also increase the risk of allergic reactions following re-administration.

Elderly Patients

Experience is limited in patients over 75 years of age and the benefits of EMINASE should be balanced against risk in this group.

Adverse Events

Hypotension observed occasionally soon after EMINASE administration is usually transient and is often associated with bradycardia.

Early reactions of flushing and bradycardia (usually within the first hour) as well as fever and nausea/vomiting (usually within 6 to 24 hours) have been reported but are generally not severe.

"Allergic-type" reactions, including bronchoconstriction or anaphylaxis have been reported but are uncommon and usually transient. A purpuric rash has occasionally been reported. All cases recovered spontaneously without sequelae.

The most common complication associated with EMINASE, as with other thrombolytics, is bleeding, most frequently from arterial and venous puncture sites. Haemoptysis, haematuria, haematemesis and malaena have been reported occasionally. Cerebrovascular accidents have been reported but the incidence is low and there has usually been a predisposing factor.

Local bleeding can be controlled with pressure. In cases of severe, uncontrolled bleeding, tranexamic acid or aprotinin should be given by slow intravenous injection to stop the fibrinolytic activity of EMINASE. Additionally, cryoprecipitate, purified clotting factor concentrates or fresh whole blood may be used to correct the haemostatic deficiency. If the haematocrit has fallen significantly, a blood transfusion may be necessary.

Reperfusion-associated arrhythmias have been reported following EMINASE treatment. These are generally transient but if prolonged they can be controlled with appropriate therapy.

Availability

IV Injection Pack:

1 vial EMINASE 30 Units, a 5ml ampoule of Water for injections B.P., a 5ml disposable syringe and needle.

Storage and Stability

EMINASE should be stored in a refrigerator (2°-8°C) and must not be used after the expiry date printed on the pack and vial, EMINASE vials must not be stored at room temperature.

Further information is available on request.

EMINASE is a product of research from Beecham Pharmaceuticals, a part of SmithKline Beecham Pharmaceuticals, Brentford, England.

EMINASE and the cardiovascular logo are trade marks.

Prescribing Information revised November 1990.

488/EMU/01/90

SmithKline Beecham
Pharmaceuticals



INJECT SURVIVE



- Simple 2 to 5 minute i.v. injection
- Rapid onset of action
- Long plasma half-life ensures prolonged thrombolysis

- Improved survival – 42.7% odds reduction in 1-year mortality¹
- Significant myocardial salvage²
- Low rate of reocclusion^{3,4}

References

1. AIMS Trial Study Group, *Lancet* 1990; **335**:427-431.
2. Bassand JP et al, *J Am Coll Cardiol* 1989; **13**:988-997.
3. Anderson JL et al, *J Am Coll Cardiol* 1988; **11**:1153-63.
4. Bonnier JJRM et al, *Am J Cardiol* 1988; **62**:25-30.

NEW

EMINASE

ANISTREPLASE

ANISOYLATED LYS-PLASMINOGEN STREPTOKINASE ACTIVATOR COMPLEX (APSAC)



simply practical thrombolysis

SB

SmithKline Beecham
Pharmaceuticals

For prescribing information see overleaf

128/EM

ANNALS OF SAUDI MEDICINE

TABLE OF CONTENTS

Volume 11 Number 3

May 1991

EDITORIAL

Treating Children with Chronic Renal Failure: A Perspective

Tej K. Mattoo 253

ORIGINAL ARTICLES

The Pattern and Outcome of Burn Injuries at a Burn Unit in Saudi

Arabia: Retrospective Analysis of Consecutive 501 Patients

Mohammed M. Hegazy, Ezzeldin M. Ibrahim 255

Patterns of Accidental Fractures and Dislocations in Children in Riyadh, Saudi Arabia

Abdulhalim A. Badr 260

Pena-Shokeir Phenotype: A Lethal Pattern of Multiple Congenital Anomalies

Ahmed Warda, Hassan Abduljabbar, Hassan Ghafouri, Abdullah H. Basalamah 264

Incidence of Major Infection in Sick Cell Pediatric Patients at Qatif Central Hospital

Hussain Ali Abu-Srair, Ali Magzoub El-Bashier,
Ibrahim S. Al-Dabous, Mohamed Al-Khater 267

Morphological and Immunologic Pattern of Blastic Transformation in Chronic Myeloid Leukemia
in Saudi Arabia: Study of 90 Transformations Among 248 Patients

George T. Roberts, M. Andrew Padmos, Hugh Clink,
David G. Spence, Peter Ernst, Kirtikant V. Sheth 271

Current Procedures for Bladder Substitution and Urinary Diversion at

King Faisal Specialist Hospital and Research Centre

Torsten Sundin, Shahid Rafiq, Bo Johan Norlen, Göran Alhgren 276

Pattern of Cancer at Asir Central Hospital, Abha, Saudi Arabia

Abdur Rauf Khan, Nazir K. Hussain, Abdulaziz Al-Saigh,
Tarek Malatani, Anwar A. Sheikha 285

Hypercalcemia in Active Pulmonary Tuberculosis

Sulaiman A. Al-Majed, Riad Sulimani, Faisal Al-Kassimi,
Lalit Pandya, Sameer Huraib, Nasser Al-Sharif 289

Pulmonary Tuberculosis in Diabetic Patients

Lalit Pandya, Nasser Al-Sharif, Ali Maraey, Sulaiman Al-Majed, Mahmood El-Sakka 293

Acute Renal Failure in Neonates: A Prospective Study

Howaida M.A.M. Al Idressy, Omer B. Abdel Basit, Khalid N. Haque,
Murtala B. Abdurrahman 297

Insulin-Dependent Diabetes Mellitus in Children: Familial and Clinical Patterns in Riyadh

Hussein Salman, Ahmed Abanamy, Basset Ghassan, Mohammed Khalil 302

Meningitis in Children of Elmadina Elmunawara

Eisa Osman El-Amin, El-Fatih El-Shiek Musa, Sabah Ali Yousif 307

Measles Vaccine Failure

Ahmed Abanamy, Mohammed Khalil, Hussein Salman, Mahmoud Abdulazeem 311

Mantoux Reaction Survey Conducted in the Northern Region of Saudi Arabia

Feisal Al-Kassimi, Anwar Abdullah, Ibrahim Al-Orainey,
Mohamed Al-Hajjaj, Essam Al-Deen Abdul Baghee, Abdul-Baree Baner 315

Urinary Tract Infection in Pregnancy

Hassan Abduljabbar, Rajaa A. Moumena, Hisham A. Mosli,
Ahmed S. Khan, Ahmed Warda 322

SPECIAL COMMUNICATIONS

Evaluation of Students' Performance and Examination Procedures in
Final Certifying Examinations in Internal Medicine (1982-1988)

Ezzeldin M. Ibrahim, Hassan Y. Al-Idrissi, Hussain M. Al-Freih,
Yussuf M. Al-Gindan 325

An Appraisal of the Utilization of Antenatal Services in Primary Health Care

Abdulaziz Nasser Al-Nasser 331

Public Attitude and Accessibility Concerning Kidney Donation Card
and Living Related Donation in Riyadh, Saudi Arabia

Sulaiman Al-Shammari 336

Volume 11, Number 4, July 1991
Dhu Al-Hijjah 1411

ANNALS
of Saudi Medicine

ACT FAST WITH ACTILYSE



Actilyse
alteplase
tissue plasminogen activator

In acute MI time is critical. Heart attack victims need emergency facilities and treatment without delay. Now, many hospitals across the country are using new therapies to treat heart attacks – therapies that must be given as early as possible in the course of an attack to minimize heart muscle damage.

Early thrombolytic treatment with Actilyse dissolves clots in blocked coronary arteries resulting in rapid and effective reperfusion of ischaemic myocardium¹. Clinically this results in improvement in LV function², reduction in infarct size³, fewer cardiac complications⁴ and, above all, reduction in mortality⁵.

Actilyse is nature's own protein, without allergic or antigenic potential⁶ that does not react with antistreptococcal antibodies. In the emergency room infusion related hypotension is minimised and the short half life and fibrin specificity make Actilyse treatment compatible with other invasive interventions like angioplasty or emergency CABG.

Consider Actilyse. Nature's own life-saving thrombolytic that opens arteries fast. Because in acute MI, every minute counts.

References

1. TIMI Study Group N Engl J Med 1985; 312 (13) 932
2. Guerri AD N Engl J Med 1987; 317: 1613-1618
3. Aust. Nat. Study Lancet 1988; 1: 203-207
4. O'Rourke M Circulation 1988; 77: (6) 1311-1315
5. Van de Werf J AM Coll Cardiol 1988; 12: 14A-9A
6. de Bono DP Pharm Jour 1985; 54-55



**Boehringer
Ingelheim**



P.O. Box 463, Jeddah 21411
Kingdom of Saudi Arabia

Full prescribing information available upon request.

Volume 11, Number 4, July 1991
Dhu Al-Hijjah 1411

ANNALS of Saudi Medicine

EDITORIAL BOARD

MOHAMMED AKHTAR, MD, FCAP, EDITOR-IN-CHIEF

MAGID AMER, MD, FRCS(E), FRCP(C), FACP

ABDUL AZIZ AL-MESHARI, FRCOG

CARLOS G. DURAN, MD, PhD

MANSOUR AL-NOZHA, MB, BS, FRCP(LOND), FRCP

SALAH R. AL-FAQIH, MB, ChB, FRCS (GLASG), FRCS (ENGLAND)

KHALID F. TABBARA, MD

NADIR FARID, MBBS, FRCP(LOND), FRCP(C), FACP

SAADI TAHER, FRCP

M. ZUHEIR AL-KAWI, MD, FAAN

EDITORS

MOHAMMED AKHTAR, MD, FCAP

Editor-In-Chief

SAADI TAHER, FRCP, Administrative Editor

M. ZUHEIR AL-KAWI, MD, FAAN, Arabic Text Editor

MARY ANNE DE SANTIS, Assistant Editor

EDITORIAL ASSISTANTS

VIRGINIA J. CROSIAR

SHIRLEY M. MOFFITT

The *Annals of Saudi Medicine* is published bimonthly and is a joint project of the King Saud University College of Medicine and King Khalid University Hospital, P.O. Box 2925, Riyadh 11461, Saudi Arabia, and King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. It is typeset and printed at the King Saud University Press. The *Annals* is distributed and Arabic abstracts are prepared, in association with Dr. Zuheir Al-Kawi, by staff of the Office Services Department of the King Faisal Specialist Hospital and Research Centre. All correspondence, reprint, and subscription information requests should be addressed to the Publications Office. Subscription price SR25 per issue.

Publications Office

Annals of Saudi Medicine

King Faisal Specialist Hospital and Research Centre

P.O. Box 3354

Riyadh 11211, Saudi Arabia

Advertising Representative:

PRC Associates

Pathrace House, 91-92 High Street

Banstead, Surrey SM 72 NL

Telephone: 0044-737-373544

Fax: 0044-737-362813

All articles published represent the opinions of the authors and do not reflect official policy of the *Annals*. All rights are reserved to the *Annals of Saudi Medicine*. No part of the journal may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or via any storage or retrieval system, without written permission from the journal.

Indexed by Current Contents, Excerpta Medica,
and Current Awareness in Biological Sciences.
ISSN 0256-4947

ANNALS OF SAUDI MEDICINE

Aims and Scope

The *Annals of Saudi Medicine* is a joint project of the King Faisal Specialist Hospital and Research Centre and the King Saud University College of Medicine and King Khalid University Hospital. The journal is typeset and printed at the King Saud University Press, Riyadh, Saudi Arabia. Since July 1985, the *Annals* has incorporated *The King Faisal Specialist Hospital Medical Journal*, established in 1980.

The *Annals* is a bimonthly multidisciplinary medical journal. High-quality papers, written in English, dealing with aspects of clinical, academic or investigative medicine or research will be welcome. Emphasis is placed on matters relating to medicine in Saudi Arabia in particular, and the Middle East in general, though articles are welcome from anywhere in the world, and the *Annals* has worldwide readership.

The *Annals* publishes original articles, case reports, letters to the editor, editorials, and from time to time, special communications, commentaries, and review articles. Abstracts of meetings and symposia sponsored by the Joint Board for Postgraduate Medical Education of Saudi Arabia are published, and the proceedings of such symposia may be published if the Editorial Board considers them appropriate and relevant. The Editorial Board wishes to minimize delay between manuscript submission, decision, and publication, and accordingly authors are requested to follow carefully the instructions set out under "Information for Authors."



King Saud University Press – 1411 A.H.

ADVISORY BOARD

J. P. Blandy, MA, DM, MCh, FRCS, FACS
The London Hospital and St. Peter's Hospital
London, England, UK

Robert M. Blizzard, MD
Professor of Pediatrics
Director, Children's Medical Center
University of Virginia School of Medicine
Charlottesville, Virginia, USA

G. J. Ebrahim, FRCP(E), FRCP(GLASG)
Reader in Tropical Child Health
Institute of Child Health
University of London
London, England, UK

**Alan E. H. Emery, MD, PhD, DSc, FRCP(E),
MFCM, FRCS(E)**
Emeritus Professor of Human Genetics
University of Edinburgh
Edinburgh, Scotland, UK

Gilbert H. Fletcher, MD
Professor of Radiotherapy
Division of Radiotherapy
The University of Texas System Cancer Center
M.D. Anderson Hospital and Tumor Institute
Houston, Texas, USA

Richard J. Glascock, MD
Professor and Chairman
Department of Medicine
Harbor-UCLA Medical Center
UCLA School of Medicine
Torrance, California, USA

Richard L. Goode, MD
Professor of Surgery
Division of Otolaryngology and
Head and Neck Surgery
Stanford Medical Center
Stanford, California, USA

Bertron M. Groves, MD
Associate Professor of Medicine
Director, Cardiac Catheterization Laboratory
University of Colorado Health Sciences Center
Denver, Colorado, USA

John Bernard Henry, MD
President
State University of New York Health
Science Center at Syracuse
Syracuse, New York, USA

Howard W. Jones, III, MD
Director of Gynecologic Oncology
Professor of Obstetrics and Gynecology
Vanderbilt University
Nashville, Tennessee, USA

David N. S. Kerr, MB, ChB, MSc, FRCP, FRCP(E)
Dean, Royal Postgraduate Medical School
Hammersmith Hospital
London, England, UK

Ronald D. Miller, MD
Professor and Chairman of Anesthesia
Professor of Pharmacology
University of California, San Francisco
San Francisco, California, USA

J. P. Mohr, MD
Sciarras Professor of Clinical Neurology
Neurological Institute
College of Physicians & Surgeons of Columbia University
New York, New York, USA

William L. Nyhan, MD, PhD
Professor and Chairman
Department of Pediatrics
School of Medicine
University of California, San Diego
La Jolla, California, USA

Roy M. Pitkin, MD
Professor and Chairman
Department of Obstetrics and Gynecology
UCLA School of Medicine
Los Angeles, California, USA

P. P. Rickham, MD, MS, FRCS, FRACS, DCH
Professor, Department of Pediatric Surgery
Universitätskinderklinik
Zurich, Switzerland

Fred S. Rosen, MD

James L. Gamble Professor of Pediatrics
(Harvard Medical School)
The Children's Hospital
Boston, Massachusetts, USA

Robert W. Schrier, MD

Professor and Chairman
Department of Medicine
Head, Division of Renal Diseases
University of Colorado School of Medicine
Denver, Colorado, USA

Norman E. Shumway, MD, PhD

Frances and Charles D. Field Professor and
Chairman, Department of Cardiovascular Surgery
Stanford University School of Medicine
Stanford, California, USA

Harlan J. Spjut, MD

Fulbright Professor of Pathology
Department of Pathology
Baylor College of Medicine
Houston, Texas, USA

**Miltiadis A. Stefadouros, MD, FACP, FACC,
FCCP, FACA, FAHA**

Professor of Medicine (Cardiology)
Chairman, Department of Medicine
King Fahad Hospital
Saudi Arabian National Guard
Riyadh, Saudi Arabia

A. J. Strong, MA, FRCS(E)

Consultant Neurosurgeon
The Neurosurgical Unit
Guy's, Maudsley and
King's College Hospitals
De Crespigny Park
London, England, UK

William B. Strong, MD

Charbonnier Professor of Pediatrics
Chief, Section of Pediatric Cardiology
Medical College of Georgia
Augusta, Georgia, USA

P. K. Thomas, DSc, MD, FRCP

Professor of Neurology
Institute of Neurology
Royal Free Hospital School of Medicine
University of London
London, England, UK

John A. Washington, II, MD

Chairman, Department of Microbiology
The Cleveland Clinic Foundation
Cleveland, Ohio, USA

**Graham H. Whitehouse, MB,BS, FRCP,
FRCR, DMRD, AKC**

Professor of Diagnostic Radiology
University of Liverpool
Liverpool, England, UK

ANNALS OF SAUDI MEDICINE

TABLE OF CONTENTS

Volume 11 Number 4

July 1991

EDITORIAL

Vale

Peter B. Herdson	365
------------------------	-----

ORIGINAL ARTICLES

Fine-Needle Aspiration Biopsy Diagnosis of Pediatric Neoplasms	
Mohammed Akhtar, M. Ashraf Ali, Anwaar Burgess, Mahmuda Huq, Mohammed Bakry	366
Fistula-In-Ano: A Pathological Study	
Jehoram T. Anim, Saleh A. Sawayan, Chris S. Grant, Hassan Al-Breiki	377
Jeddah Experience in the Management of High Anal Fistula	
Adnan Mohamed Rashid Jamjoom, Yasir Saleh Jamal	381
The Management of Anorectal Abscess: An Inexpensive and Simple Alternative Technique to Incision and "De-roofing"	
William H. Isbister, Stephen Kyle	385
Pancreatic Pseudocyst: A Review of 5 Years' Experience	
Saleh Hamza Al-Sulaimani, Mohammed Khurshid Alam	391
Damage to the Bile Ducts at Cholecystectomy	
Tarek Said Malatani	396
Surgical Management of Chiari Malformation and Syringomyelia: Experience in 14 Cases	
Naim-Ur-Rahman, Zain Alabedeen B. Jamjoom	402
The Value of Oligoclonal Bands in Neurobrucellosis	
Abdul Kader Daif	411
Comparative Responses of Plasma Glucose, Insulin and C-Peptide Following Ingestion of Isocaloric Glucose, a Modified Urban Saudi Breakfast and Dates in Normal Saudi Persons	
Mohammed Ahmed, Abdulaziz Al Othaimeen, Edward De Vol, Alan Bold	414
Lipoid Proteinosis: Clinical, Genetic and Pathologic Study of a Saudi Arabian Family	
Mirghani A. E. Uthman, Mohamed B. Satti, Mohamed E. Baraka	418
Use of Gas Liquid Chromatography as an Adjunct to Conventional Bacteriological Methods in the Diagnosis of Anaerobic Cerebral Abscess	
Sabiha Pit, Farida Jamal, Fadzli K. Cheah, Mohammed Ariff Mohammed Abbas	424
Bacteriuria, Incidence, Causative Microorganism, and Susceptibility Pattern at Qatif Central Hospital	
Ali Magzoub El-Bashier	429
Helicobacter Pylori and Chronic Gastritis	
Khalid Mahmood	435
Increasing Compliance Over Five Years in a Hepatitis B Infant Immunization Program in Saudi Arabia	
Frank W. Kiel	439
Pulmonary Tuberculosis in Saudi Arabia: A Retrospective Study of 1566 Patients	
Mohammed Saleh Al-Hajjaj, Lalit Pandya, Ali A. Marie, Abdul Aziz Madani, Nasser Al-Sharif, Sulaiman Al-Majed	443
IgE-Mediated Skin Reaction Among Asthmatic Children in Riyadh	
Abdulrahman Al Frayh	448



AUGMENTIN clavulanate-potentiamed amoxycillin. **INDICATIONS.** **Upper Respiratory Tract Infections** e.g. Sinusitis, tonsillitis, otitis media. **Lower Respiratory Tract Infections** e.g. Acute and chronic bronchitis, lobar and bronchopneumonia, empyema, lung abscess. **Skin And Soft Tissue Infections** e.g. Boils/abscesses, cellulitis, wound infections, intra-abdominal sepsis. **Genito-Urinary Infections** e.g. Cystitis, urethritis, pyelonephritis, septic abortion, puerperal sepsis, pelvic infections, chancroid, gonorrhoea. **Other Infections** e.g. Osteomyelitis, septicaemia, peritonitis, post-operative infections. AUGMENTIN intravenous is also indicated for prophylaxis against infections which may be associated with major surgical procedures involving gastro-intestinal, pelvic, head and neck, cardiac, renal, biliary tract and joint replacement surgery. **DOSAGE. Adults and Children over 12 years** IV injection/infusion – Usually 1.2g 8 hourly. In more serious infections increase frequency to 6 hourly intervals. **Children** IV injection/infusion – Children 3 months-12 years: Usually 30mg/kg* AUGMENTIN infusion 8 hourly. In more serious infections, increase frequency to 6 hourly intervals. Children 3 months-30 months: 30mg/kg* AUGMENTIN every 12 hours in premature infants and in full term infants during the perinatal period, increasing to 8 hourly intervals thereafter. *Each 30mg AUGMENTIN intravenous contains 25mg amoxycillin and 5mg clavulanic acid. Treatment with AUGMENTIN should not be extended beyond 14 days without review. **CONTRA-INDICATION.** Penicillin hypersensitivity. **PRECAUTIONS.** Changes in liver function tests have been observed in some patients receiving AUGMENTIN. The clinical significance of these changes is uncertain but intravenous AUGMENTIN should be used with caution in patients with evidence of severe hepatic dysfunction. In patients with moderate or severe renal impairment AUGMENTIN dosage should be adjusted as recommended in the Package Insert Leaflet. **USE IN PREGNANCY AND LACTATION.** Use of AUGMENTIN in pregnancy is not recommended unless considered essential by the physician. During lactation, trace quantities of penicillins can be detected in breast milk. **SIDE-EFFECTS.** Side-effects, as with amoxycillin, are uncommon and mainly of a mild and transitory nature. Diarrhoea, pseudomembranous colitis, indigestion, nausea, vomiting.

bacteria that defeat most ordinary antibiotics, allowing it to replace standard combination therapies.¹⁻⁹

Which makes it an outstandingly powerful and reliable antibiotic.

An antibiotic that can simplify the management of clinical and surgical infection.

IV Augmentin is highly

Demonstrating consistent and outstanding clinical success in the treatment of both aerobic and anaerobic infection, including *Bacteroides*.²

Making it a powerful single choice for the first-line treatment of infection or reliable surgical prophylaxis.³⁻¹⁰



d candidiasis have been reported. Phlebitis at the site of injection has also been reported. Urticarial and erythematous rashes sometimes occur but their incidence has been particularly low in clinical trials. An urticarial rash suggests penicillin hypersensitivity and treatment should be discontinued. Erythematous rashes are frequently mild and transient but may be severe when associated with infectious mononucleosis, in which case treatment should be discontinued. Rare cases of erythema multiforme, Stevens-Johnson syndrome and an occasional case of exfoliative dermatitis have been reported. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Hepatitis and cholestatic jaundice have been reported. **AVAILABILITY:** 600mg AUGMENTIN intravenous vial, each containing 500mg amoxycillin and 100mg clavulanic acid. 1.2g AUGMENTIN intravenous vials: Each containing 1g amoxycillin and 200mg clavulanic acid. In IV presentations amoxycillin is present as the sodium salt and clavulanic acid is present as the potassium salt. Each 1.2g vial contains approximately 1.0 mmol of potassium and 3.1 mmol of sodium. Not all presentations are available in every country. Further information is available on request from SmithKline Beecham Pharmaceuticals International, Brentford, England. AUGMENTIN is a product of research from Beecham Pharmaceuticals International, Brentford, England. Augmentin is a trade mark. **REFERENCES:** 1. Green-Thompson RW et al, *Proc 13th ICC Vienna* 1983; **(79):** 17. 2. Abbas AMA et al, *Excerpta Medica* 1980; **ICS 544:** 173. 3. Tehan S, Whittaker J, *Surg Res Commun* 1989; **6:** 97. 4. Levi D et al, *Pharmatherapeutica* 1989; **5:** 355. 5. Whittaker J, Tehan S, *J Drug Dev* 1989; **2** (Suppl 1): 71. 6. Asbach HW et al, *Proc 13th ICC Vienna* 1983; **70:** 30. 7. Croydon EAP et al, *Chemotherapie* 1985; **4** (Suppl 2): 168. 8. Martini M et al, Data on file, Beecham Pharmaceuticals. 9. Ploechl E, Huber EG, *J Int Med Res* 1986; **14** (3): 153. 10. Drumm J et al, *Br J Surg* 1985; **72** (7): 571.

Beecham
Pharmaceutical
BRENTFORD ENGLAND

001/3/1/178/9

SPECIAL COMMUNICATION

Nursing: Attitudes, Perceptions and Strategies for Progress in Saudi Arabia

Cynthia L. Jackson, Rebecca Gary 452

CASE REPORTS

Gluteal Necrosis with Ano-Gluteal Fistula: A Result of Umbilical

Artery Catheterization

A. Latif Al-Arfaj, Mohammed S. Khwaja 459

Abdominal Cocoon in a Pregnant Woman: A Case Report and Review of the Literature

Kamal I. Ali Gharaibeh, N.A. Morad, E. Sunna 462

Hepatic Cystadenoma with Mesenchymal Stroma (CMS): Report of Case

Presenting With Obstructive Jaundice

Mohamed B. Satti, Abdulaziz A. Al-Quorain, Majed S. Al-Awami,
Abdulla Y. El-Hassan, Ghassab Al-Ghassab, Abdul Aziz Al-Jamaa 465

The Budd-Chiari Syndrome: A Case Report and Review of Current

Management Options

Mohamed A. Al-Karawi, Abdul M. Ahmed, Abdel Rahman El-Shiekh Mohamed 471

Hereditary Pyropoikilocytosis: A Case Report with Thermal Studies

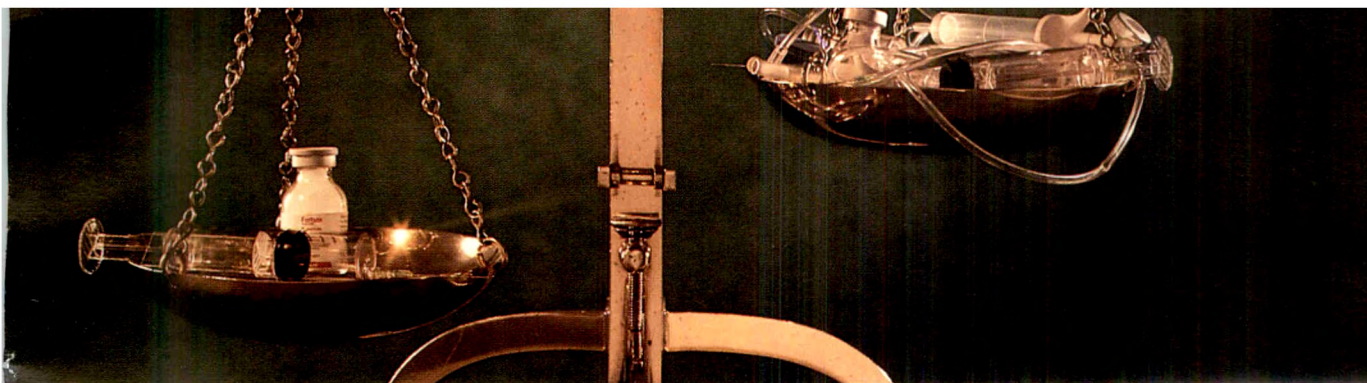
and Scanning Electron Microscopy

Salim H. Khalil, Randa M. Nounou 475

LETTERS TO THE EDITOR 478

ANNOUNCEMENTS 487

CORRECTION 488



The choice is simple

Fortum provides the extended spectrum required for monotherapy without the ototoxic and nephrotoxic side effects of aminoglycoside combinations.

Fortum is a simple and effective approach to hospital acquired infections.

FORTUM

CEFTAZIDIME

Abbreviated Prescribing Information

Presentation: Fortum for injection is supplied in vials containing 250 mg, 500 mg, 1 g and 2 g ceftazidime (as pentahydrate) with sodium carbonate. **Uses:** Fortum is a bactericidal cephalosporin antibiotic which is resistant to most beta-lactamases and is active against a wide range of Gram-positive and Gram-negative bacteria. It is indicated for the treatment of single infections and for mixed infections caused by two or more susceptible organisms. Fortum, because of its broad antibacterial spectrum, may be used alone as first choice drug, pending sensitivity test results. **Dosage and administration:** Adults: 1 g to 6 g i.m. or i.v. per day and by the i.p. route 125 to 250 mg per two litres of dialysis fluid (see Data Sheet for details). Neonates, Infants and Children: Up to two months: 25 to 60 mg/kg/day given as two divided doses has proved to be effective. In the neonate the serum half-life of ceftazidime can be three to four times that in adults. Over two months: 30 to 100 mg/kg/day given as two or three divided doses (see Data Sheet for details). In Impaired Renal Function: the dosage of ceftazidime should be reduced when the glomerular filtration rate (GFR) falls below 50 ml/min. An initial loading dose of 1 g may be given to patients with suspected renal insufficiency (See Data Sheet for details). **Contra-indication:** Fortum is contra-indicated in patients with known hypersensitivity to cephalosporin antibiotics. **Precautions:** Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins. Care is indicated in patients who have experienced an anaphylactic reaction to penicillin. Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with nephrotoxic drugs. Clinical experience with Fortum has shown that this is not likely to be a problem at the recommended dose levels. As with all drugs, Fortum should be administered with caution during the early months of pregnancy and in early infancy. Fortum is excreted in human milk in low concentrations. Fortum does not interfere with enzyme-based tests for glycosuria. Slight interference with copper reduction methods may be observed. Fortum does not interfere in the alkaline picrate assay for creatinine. Fortum and aminoglycosides should not be mixed in the same giving set or syringe. As with other broad spectrum antibiotics, prolonged use of Fortum may result in the overgrowth of non-susceptible organisms (e.g., *Candida*, *Enterococci*) which may require interruption of treatment or adoption of appropriate measures. **Side effects:** Fortum is generally well tolerated with only infrequent adverse reactions, e.g. pain and/or inflammation after i.m. administration and phlebitis and/or thrombophlebitis after i.v. administration, rashes, fever, pruritus, anaphylaxis, gastrointestinal disturbances, headache, dizziness, paraesthesia and bad taste. Transient changes in laboratory values may occur including: eosinophilia, a positive Coombs' test, thrombocytosis, leucopenia, thrombocytopenia and slight rises in hepatic enzymes.

Glaxo For full prescribing information see data sheet or contact: **Glaxomed Limited**, International House, 7 High Street, Ealing, London W5 5DB, ENGLAND

Fortum is a trade mark

Motilium

TRADEMARK

domperidon

In chronic
or recurrent
indigestion

CCM-ADV-JP 596

Full prescribing information available on request



JANSSEN
PHARMACEUTICA

The drug discovery company

Beerse · Belgium

© Janssen Pharmaceutica 1991



The choice is simple

Fortum provides the extended spectrum required for monotherapy without the ototoxic and nephrotoxic side effects of aminoglycoside combinations.

Fortum is a simple and effective approach to hospital acquired infections.

FORTUM

CEFTAZIDIME

Abbreviated Prescribing Information

Presentation: Fortum for injection is supplied in vials containing 250 mg, 500 mg, 1 g and 2 g ceftazidime (as pentahydrate) with sodium carbonate. **Uses:** Fortum is a bactericidal cephalosporin antibiotic which is resistant to most beta-lactamases and is active against a wide range of Gram-positive and Gram-negative bacteria. It is indicated for the treatment of single infections and for mixed infections caused by two or more susceptible organisms. Fortum, because of its broad antibacterial spectrum, may be used alone as first choice drug, pending sensitivity test results. **Dosage and administration:** Adults: 1 g to 6 g i.m. or i.v. per day and by the i.p. route 125 to 250 mg per two litres of dialysis fluid (see Data Sheet for details). Neonates, Infants and Children: Up to two months: 25 to 60 mg/kg/day given as two divided doses has proved to be effective. In the neonate the serum half-life of ceftazidime can be three to four times that in adults. Over two months: 30 to 100 mg/kg/day given as two or three divided doses (see Data Sheet for details). In Impaired Renal Function: the dosage of ceftazidime should be reduced when the glomerular filtration rate (GFR) falls below 50 ml/min. An initial loading dose of 1 g may be given to patients with suspected renal insufficiency (See Data Sheet for details). **Contra-indication:** Fortum is contra-indicated in patients with known hypersensitivity to cephalosporin antibiotics. **Precautions:** Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins. Care is indicated in patients who have experienced an anaphylactic reaction to penicillin. Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with nephrotoxic drugs. Clinical experience with Fortum has shown that this is not likely to be a problem at the recommended dose levels. As with all drugs, Fortum should be administered with caution during the early months of pregnancy and in early infancy. Fortum is excreted in human milk in low concentrations. Fortum does not interfere with enzyme-based tests for glycosuria. Slight interference with copper reduction methods may be observed. Fortum does not interfere in the alkaline picrate assay for creatinine. Fortum and aminoglycosides should not be mixed in the same giving set or syringe. As with other broad spectrum antibiotics, prolonged use of Fortum may result in the overgrowth of non-susceptible organisms (e.g., *Candida*, *Enterococci*) which may require interruption of treatment or adoption of appropriate measures. **Side effects:** Fortum is generally well tolerated with only infrequent adverse reactions, e.g. pain and/or inflammation after i.m. administration and phlebitis and/or thrombophlebitis after i.v. administration, rashes, fever, pruritus, anaphylaxis, gastrointestinal disturbances, headache, dizziness, paraesthesia and bad taste. Transient changes in laboratory values may occur including: eosinophilia, a positive Coombs' test, thrombocytosis, leucopenia, thrombocytopenia and slight rises in hepatic enzymes.

Glaxo For full prescribing information see data sheet or contact: **Glaxomed Limited**, International House, 7 High Street, Ealing, London W5 5DB, ENGLAND

Fortum is a trade mark

Motilium

TRADEMARK

domperidon

In chronic
or recurrent
indigestion

Full prescribing information available on request



JANSSEN
PHARMACEUTICA

The drug discovery company

Beerse · Belgium

© Janssen Pharmaceutica 1991

Editorial

VALE

This issue of the *Annals of Saudi Medicine* will appear after I have relinquished the position of Editor-in-Chief. I have held this position for more than five years, and have greatly enjoyed the diverse responsibilities which it entails.

In 1985, the *Annals* had recently become a joint responsibility of the King Faisal Specialist Hospital and Research Centre and the King Khalid University Hospital of King Saud University, having started out as the *King Faisal Specialist Hospital Medical Journal* five years before.

Initially typeset and printed by the British medical publishers, John Wright and Company of Bristol, printing of the *Annals* became the responsibility of the King Saud University Press here in Riyadh in 1985. Shortly afterwards, typesetting was undertaken jointly by the staff of the *Annals* at King Faisal Specialist Hospital and of the University Press.

In those days in the middle of 1980s we received about 100 manuscripts each year for consideration of their publication, and we produced four issues a year, each with about 8 original articles. Last year (1990) we received nearly 400 manuscripts and published about half of these in our six issues, each with at least 20 original articles.

For the past three years or so, we have carried an increasing amount of advertising, and this has received favorable comment from many readers, adding to the interest of the journal, whilst also helping to defray the considerable production costs.

The style and format of the *Annals* have been improved, with developments such as printing the contents on the outside back cover. Other planned developments include more modern and efficient plastic packaging for mailing the journal, and the inclusion of advertising inserts.

A medical journal can only be as good as the material submitted for publication. It is a pleasure to report that many of our authors view the *Annals* as a journal of first choice for their important

papers. And the standard of writing and presentation of manuscripts submitted has steadily improved over the years.

I pay tribute to the wonderful work of the full time staff of the *Annals*, a devoted small group of people who set the scene for every issue. And Mr. Moussa A. Esmail, Director of the King Saud University Press and his competent and keen staff do a magnificent job in setting up and printing each issue. Distribution is handled partly by *Annals* office staff, and partly by staff of the Office Services Department at King Faisal Specialist Hospital and Research Centre.

The *Annals* Editorial Board includes senior members of the staff of King Faisal Specialist Hospital and Research Centre and of the King Saud University College of Medicine. The Board meets fortnightly, and reviews external referees' reports on all submitted manuscripts.

All this has been possible only because of the leadership and support of Dr. Fahad Al-Abdul Jabbar, formerly Dean of the King Saud University College of Medicine, and for the past seven years Counsel and Supervisor of Executive Management and Chief Executive Director of the King Faisal Specialist Hospital and Research Centre.

In bidding "adieu," I hope the *Annals of Saudi Medicine* will continue to go from strength to strength, and one day may become a national medical journal, published monthly, reflecting the growing proficiency of medical practice and research in the Kingdom of Saudi Arabia and surrounding countries of the Middle East.

**Peter B. Herdson, MB, ChB, MedSc,
PhD,FRCPA,(Hon)FRACR**
Editor-in-Chief
Annals of Saudi Medicine
King Faisal Specialist Hospital
P.O. Box 3354
Riyadh 11211, Saudi Arabia

Original Articles

FINE-NEEDLE ASPIRATION BIOPSY DIAGNOSIS
OF PEDIATRIC NEOPLASMS

Mohammed Akhtar, MD, FACP; M. Ashraf Ali, MD, FRCPC, FCAP;
Anwaar Burgess, MT; Mahmuda Huq, AIMLS;
Mohammed Bakry, BS, MS

روجعت سلسلة من خزعات الرشف بالإبرة الرفيعة أجريت لـ ٦٣٥ طفلاً. تضمنت التشخيصات التي تم التوصل إليها لدى هؤلاء الأطفال: اللمفوم الخبيث لدى ١٣٩ طفلاً (٢١,٩٪)، داء هديجكن ٢٥ طفلاً (٣,٩٪)، ورم أورمة العصبية ٥٨ (٩,١٪)، ورم وليمز ٣٧ (٥,٨٪)، ارتشاحات ابيضاضية ٣٣ (٥,٢٪) وأورام متفرقة ٥٢ (٨,٢٪). كانت الخزعة غير تشخيصية لدى ١٧١ مريضاً (٢٦,٩٪). وقد تم وصف وإيضاح الخصائص الشكلية الخلوية لهذه الآفات بإيجاز. كما تم ربط السمات الشكلية البارزة بمظاهر التشريح المرضي النسيجي ومظاهر البنية المستدقة.

A series of fine-needle aspiration biopsies performed in 635 children were reviewed. The diagnosis rendered in these patients included malignant lymphoma in 139 (21.9%), Hodgkin's disease, 25 (3.9%); neuroblastoma, 58 (9.1%); Wilms' tumor, 37 (5.8%); Ewing's sarcoma, 32 (5.0%); rhabdomyosarcoma, 25 (3.9%); retinoblastoma, 22 (3.5%); leukemia infiltrate, 33 (5.2%); and miscellaneous tumors, 52 (8.2%). In 171 patients (26.9%), the biopsy was nondiagnostic. The cytomorphological characteristics of these lesions are briefly described and illustrated. Salient morphological features are further correlated with histological and ultrastructural appearances.

Fine-needle aspiration biopsy (FNAB) has enjoyed an ever-increasing popularity in recent years. It is being used for diagnosing a variety of benign and malignant neoplasms and other lesions. It is now used in institutions in virtually all countries of the world [1-5]. However, the experience with FNAB in the diagnosis of pediatric neoplasms is still limited [6-8]. This is primarily because an overwhelming majority of neoplasms in children are composed of relatively undifferentiated round cells which are generally difficult to characterize precisely on the basis of morphological appearance.

At King Faisal Specialist Hospital and Research Centre, FNAB has been used extensively for diag-

nosing a large variety of lesions in both adults and children. In this study, we review our experience with this technique in the diagnosis of pediatric neoplasms and describe salient morphological features helpful in arriving at a precise diagnosis.

Material and Methods

All FNABs performed between January 1980 and December 1988 were reviewed, and cases identified in which the patient was 15 years or younger. These cases were tabulated according to the diagnosis rendered. Any case in which more than one FNAB was performed was considered as a single case.

FNABs were performed without anesthesia using a fine-bore needle (22-25 gauge). Biopsies performed before January 1985 were usually performed in a conventional manner using a syringe and a handle for applying suction. After January 1987, a majority of the biopsies were performed without the syringe or suction. In this technique,

From the Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh.

Address reprint requests and correspondence to Dr. Akhtar: Department of Pathology and Laboratory Medicine (MBC-10), King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

Accepted for publication 8 October 1990.

the needle is held in the hand without the syringe. After the lesion is entered, the needle is moved in several directions and then removed [9]. This method causes a small amount of lesional tissue to enter the needle through capillary action, and is more advantageous than the conventional technique because it provides an adequate cellular yield without causing substantial artifactual distortion. Once the specimen is obtained, it is placed on glass slides and smears made. All smears in this series were air-dried and stained with Diff-Quik. For electron microscopy examination the aspirated material is fixed in 2% buffered glutaraldehyde and processed according to a previously described technique [10].

Results

Between January 1980 and December 1988, a total of 635 patients under the age of fifteen years underwent FNAB. The diagnoses rendered in these patients are given in Table 1. The most frequently diagnosed tumor was malignant lymphoma, seen in 139 (21.9%) of the patients. The second most common tumor was neuroblastoma, which was diagnosed in 58 (9.1%) of the cases. The FNAB sample was considered nondiagnostic in 171 (26.9%) patients. The material obtained was insufficient in 121 of these patients. In another 33 patients, the material obtained was extensively necrotic, thus precluding reliable interpretation. In the remaining 17 cases, these were lesional cells but the pathologist could not arrive at a diagnosis.

TABLE 1. Details of FNAB diagnosis in 635 children.

Diagnosis	No.	(%)
Malignant lymphoma	139	(21.9)
Hodgkin's disease	25	(3.9)
Neuroblastoma	58	(9.1)
Wilms' tumors	37	(5.8)
Ewing's sarcoma	32	(5.0)
Rhabdomyosarcoma	25	(3.9)
Retinoblastoma	22	(3.5)
Leukemic infiltrate	33	(5.2)
Miscellaneous tumors	52	(8.2)
Non-neoplastic conditions	41	(6.5)
Non-diagnostic	171	(26.9)

Morphological Features

We will discuss here some of the salient morphological features, as seen on the FNAB smears from various lesions, and some of these are further correlated with histological and ultrastructural appearances.

Malignant Lymphoma: An overwhelming majority of cases of malignant lymphoma in children in Saudi Arabia are of the undifferentiated type, which includes both Burkitt- and non-Burkitt-type malignant lymphomas. Histologically these tumors are characterized by a diffuse growth pattern in which the tumor cells have a high nuclear cytoplasmic ratio, high mitotic rate, and round nuclei with a small amount of cytoplasm. In addition, there are variable numbers of benign histiocytes scattered throughout the tumor, thus producing the "starry-sky" pattern (Figure 1A). The cells in Burkitt's lymphoma are relatively uniform, whereas there is more pleomorphism in non-Burkitt types. Distinguishing between the two subtypes, however, is not always possible.

In FNAB smears, the tumor cells are scattered singly and show round nuclei with one or more nucleoli. The cytoplasm is scanty to moderate in amount; it is pale blue and usually contains small uniform cytoplasmic lipid vacuoles (Figure 1B). In the background, there are large numbers of structures composed of small fragments of cell cytoplasm (lymphoreticular bodies). An important morphological feature that helps distinguish lymphoma from other round-cell malignant tumors is that, in aspirates from malignant lymphoma, there is a total lack of cell clustering. Electron microscopy preparations also reveal cells that have a high nuclear cytoplasmic ratio and are arranged singly without any cell junctions (Figure 1C). The cytoplasm contains only a few mitochondria, large numbers of free ribosomes, and scattered non-membrane-bound lipid vacuoles [6].

Ewing's Sarcoma: Ewing's sarcoma is an undifferentiated neoplasm, histologically composed of small undifferentiated round cells. The cytoplasm is relatively scanty and somewhat clear (Figure 2A). In the majority of cases, abundant cytoplasmic glycogen can be demonstrated by periodic acid-Schiff staining.

In FNAB smears, the tumor cells tend to be uniform and are usually arranged in relatively small tight clusters. The cytoplasm is pale blue and con-

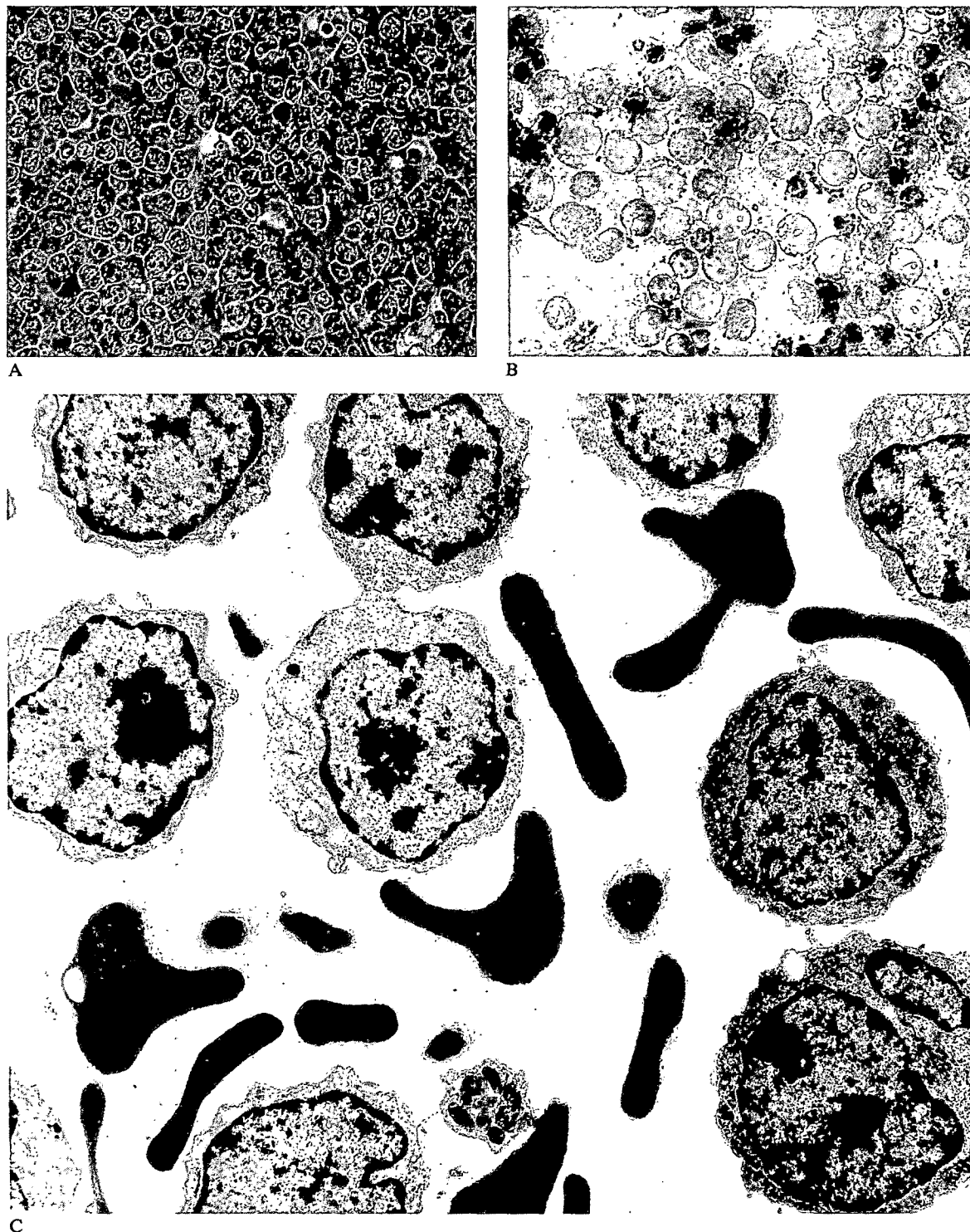


FIGURE 1. (A) Histological section showing undifferentiated Burkitt's lymphoma. (Hematoxylin-eosin stain; original magnification, $\times 250$.) (B) Aspiration smear showing undifferentiated Burkitt's lymphoma. The tumor is composed of uniform cells without any clusters. The cytoplasm of the tumor cells contains uniform round lipid vacuoles. (Diff-Quik; original magnification, $\times 250$.) (C) Electronmicrograph showing representative tumor cells from undifferentiated (Burkitt's) lymphoma. The cells are disposed individually and there are no intercellular junctions. (Uranyl acetate and lead citrate; original magnification, $\times 3500$.)

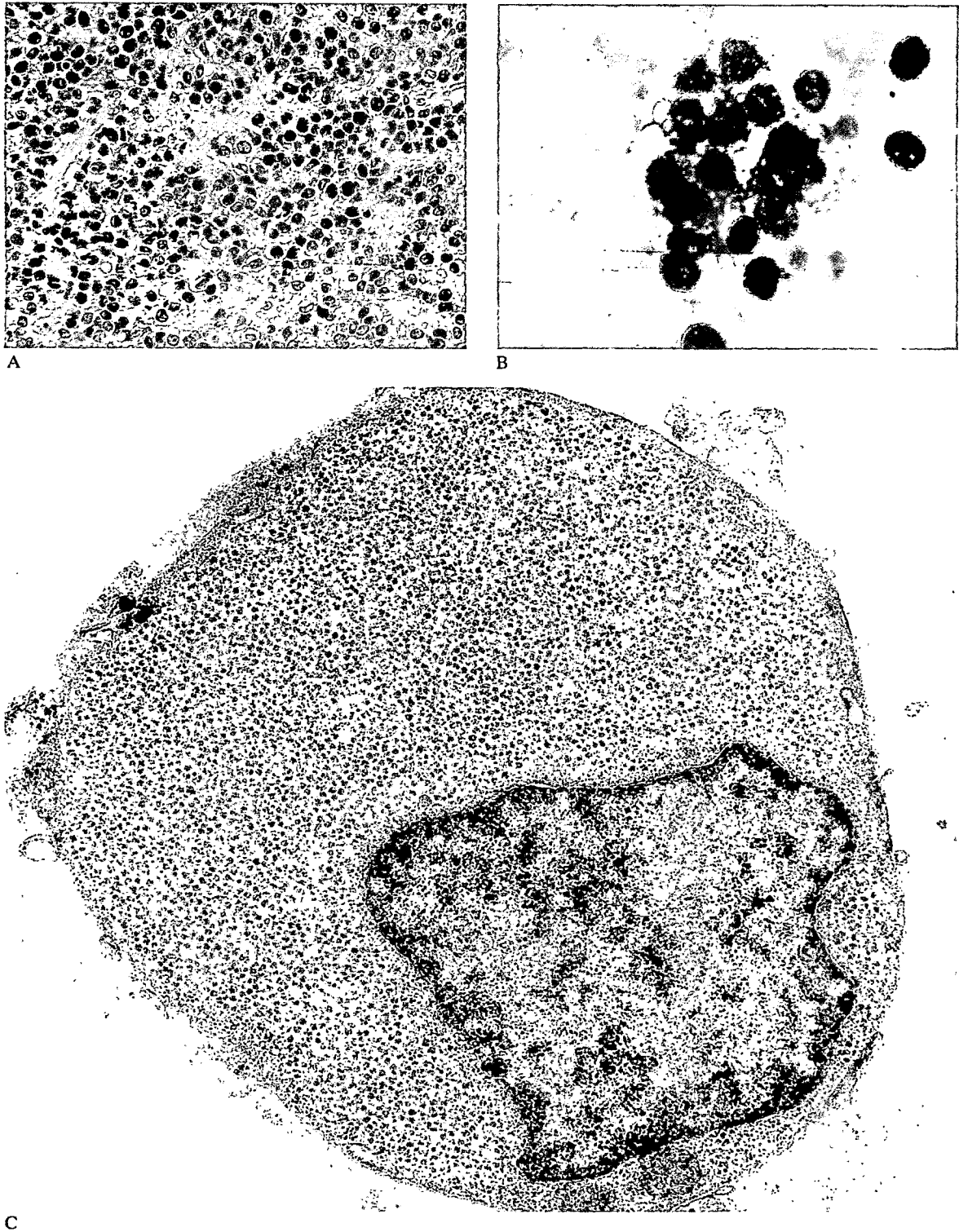


FIGURE 2. (A) Histological section showing Ewing's sarcoma. (Hematoxylin-eosin; original magnification, $\times 200$.) (B) Aspiration smear from Ewing's sarcoma showing small clusters composed of uniform cells. Some of the cells have well-defined "punched out" clear cytoplasmic vacuoles. (Diff-Quik; original magnification, $\times 300$.) (C) A tumor cell from Ewing's sarcoma in which a large amount of glycogen is present within the cytoplasm. (Uranyl acetate and lead citrate; original magnification, $\times 17600$.)

tains variable numbers of large clear "punched out" vacuoles (Figure 2B). Some of these vacuoles almost entirely replace the cytoplasm. The vacuoles correspond to the deposits of glycogen. Electron microscopy examination also confirms the presence of glycogen in areas corresponding to the cytoplasmic vacuoles (Figure 2C). In addition, there may be scattered cell junctions, but usually no cytoplasmic filaments or any neurosecretory granules are present [6,11].

Rhabdomyosarcoma: Rhabdomyosarcoma is a highly malignant neoplasm in which there is variable rhabdomyoblastic differentiation of the tumor cells. Histologically the tumor cells may vary from small undifferentiated round cells to large pleomorphic cells with abundant eosinophilic cytoplasm (Figure 3A). Some of these large cells may show cross-striation. The nuclei are relatively large and may show marked pleomorphism.

Aspiration smears from this tumor reveal cells that vary considerably in size and shape but usually contain moderate to abundant amounts of cytoplasm which stains deep blue and contains occasional small cytoplasmic vacuoles (Figure 3B). Within the cytoplasm of some of the tumor cells are ill-defined, relatively dense inclusions. The tumor cells are usually arranged singly, although occasional loose cell clusters may also be found. Electron microscopy examination of the tumor cells reveals cytoplasm that is usually rich in organelles, especially rough endoplasmic reticulum and mitochondria. In addition, some of the tumor cells contain aggregates of thick (myosin) and thin (actin) filaments arranged in parallel bundles (Figure 3C). Around these bundles is electron-dense, Z-band-like material. The cell membrane may be partly surrounded by basal lamina. The nucleus is usually large with a prominent nucleolus [6,12,13].

Neuroblastoma: Neuroblastoma is a malignant tumor composed of primitive neuroblasts derived from the sympathetic nervous system. Histologically the tumor is composed of undifferentiated round cells that are separated by variable amounts of eosinophilic fibrillary material composed of complex tangles of cytoplasmic processes derived from the tumor cells (Figure 4A). In some cases, the tumor contains pseudorosettes which consist of tumor cells arranged along the periphery and

enclosing eosinophilic fibrillary material toward the center.

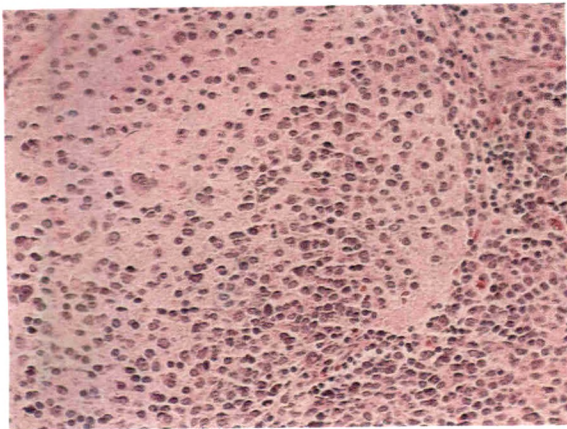
In aspiration smears from neuroblastoma, the tumor cells may be disposed singly or arranged in small clusters. The cells are small and undifferentiated with a high nuclear to cytoplasmic ratio. Small clusters of cells may be separated by pale blue to deep pink to light purple fibrillar material (Figure 4B). Structures corresponding to the pseudorosettes seen in histological sections may also be recognized. These findings may be further correlated with ultrastructural characteristics. The tumor cells usually reveal large numbers of cytoplasmic processes containing longitudinally arranged microtubules and scattered neurosecretory granules (Figure 4C). The tumor cells and cell processes have large synaptic cell junctions [6,14-17].

Wilms' Tumor: Wilms' tumor is a malignant tumor of the kidney which morphologically resembles embryological renal tissues. Histologically, it is composed of undifferentiated (blastemal) tissue which exhibits varying degrees of epithelial, tubular, and mesenchymal differentiation (Figure 5A).

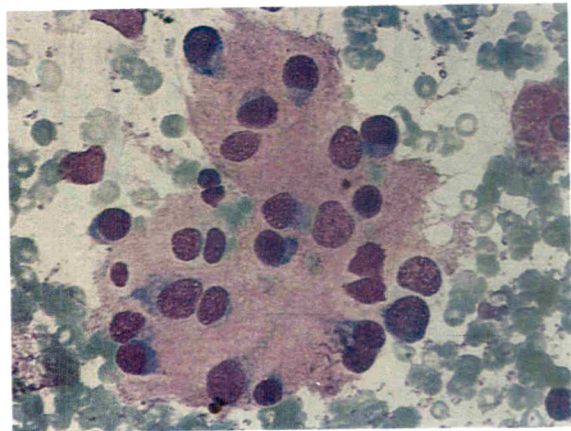
Aspiration smears from most of the cases of Wilms' tumor reveal sheets and clusters of small undifferentiated cells in which there are scattered large, pale-staining cells disposed in a random fashion. Tubular differentiation is represented by a circular arrangement of larger pale-staining epithelial cells with smaller more undifferentiated cells at the periphery (Figure 5B). Mesenchymal elements are usually composed of spindle-shaped cells, although occasional large pleomorphic cells with abundant cytoplasm may be seen. These usually represent rhabdomyosarcomatous elements [6,18]. Ultrastructurally, the cells show frequent intercellular junctions and variably developed basal lamina (Figure 5C).

Retinoblastoma: Retinoblastoma is an embryological tumor that originates from the retina. Histologically this tumor exhibits undifferentiated cells that are usually arranged to form characteristic Western-Steiner (true) rosettes (Figure 6A).

Cytological smears reveal small markedly undifferentiated cells with frequent mitosis. In addition, there is evidence of tumor-tumor cell phagocytosis. Well-defined structures corres-



A

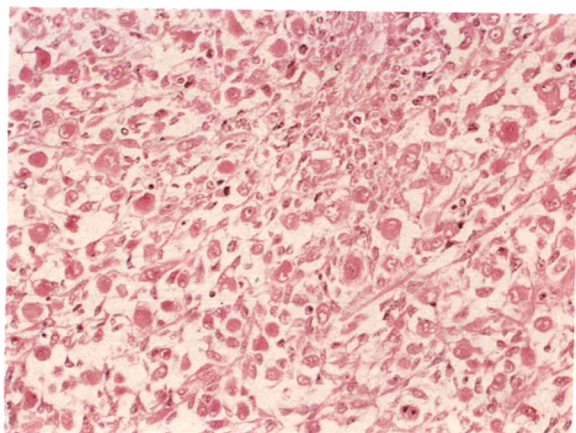


B

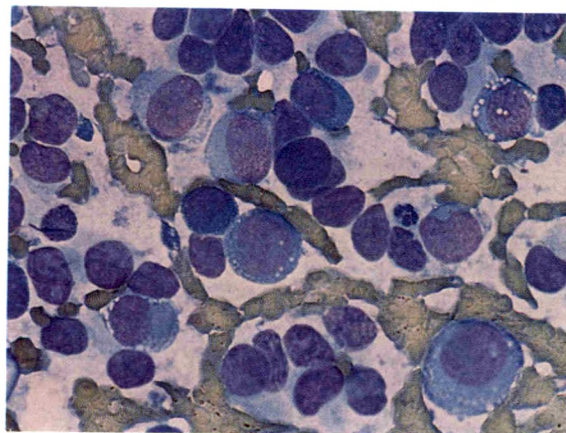


C

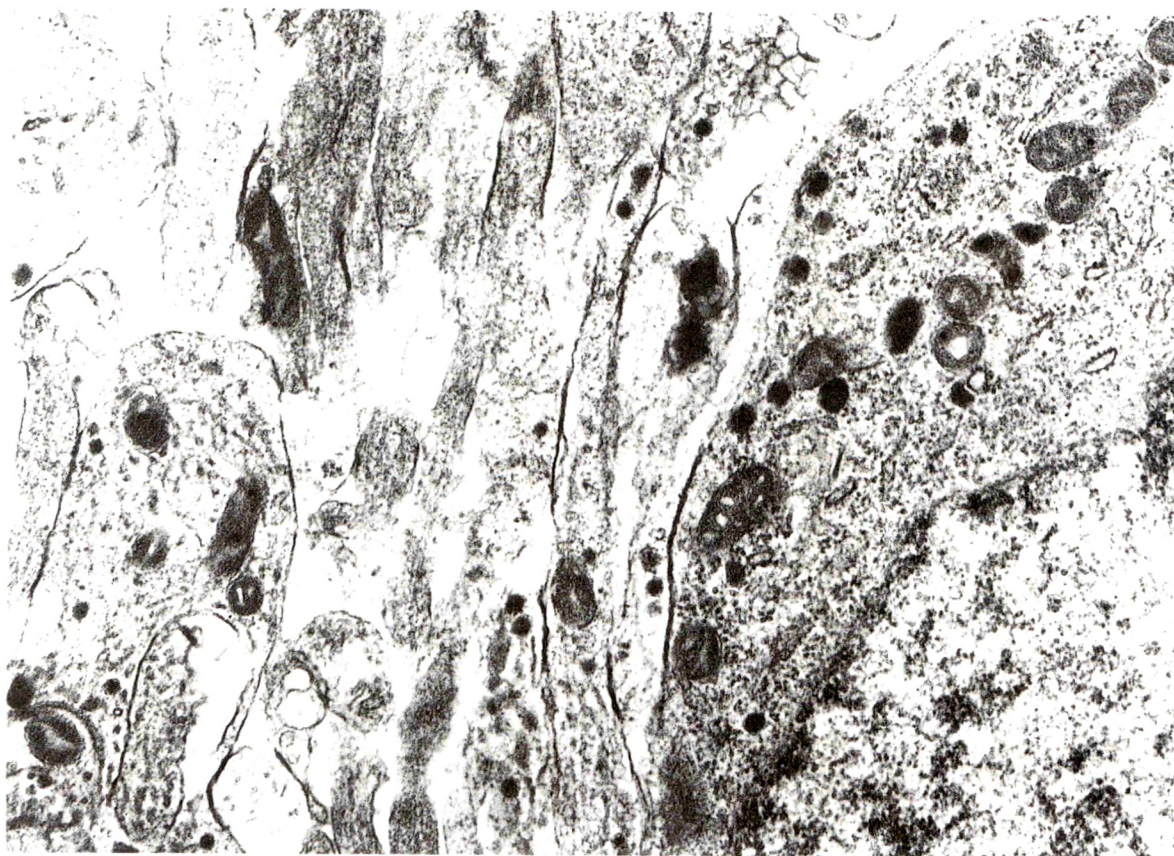
FIGURE 3. (A) Histological section from rhabdomyosarcoma featuring large cells with moderate to abundant eosinophilic cytoplasm and marked nuclear pleomorphism. (Hematoxylin-eosin; original magnification, $\times 150$.) (B) Cytological smear from rhabdomyosarcoma showing pleomorphic cells with moderate to abundant cytoplasm. (Diff-Quik; original magnification, $\times 200$.) (C) Electronmicrograph showing a tumor cell from rhabdomyosarcoma in which parallel bundles of thick and thin filaments are present. Occasional Z-band-like structures are also present. (Uranyl acetate and lead citrate; original magnification, $\times 21500$.)



A

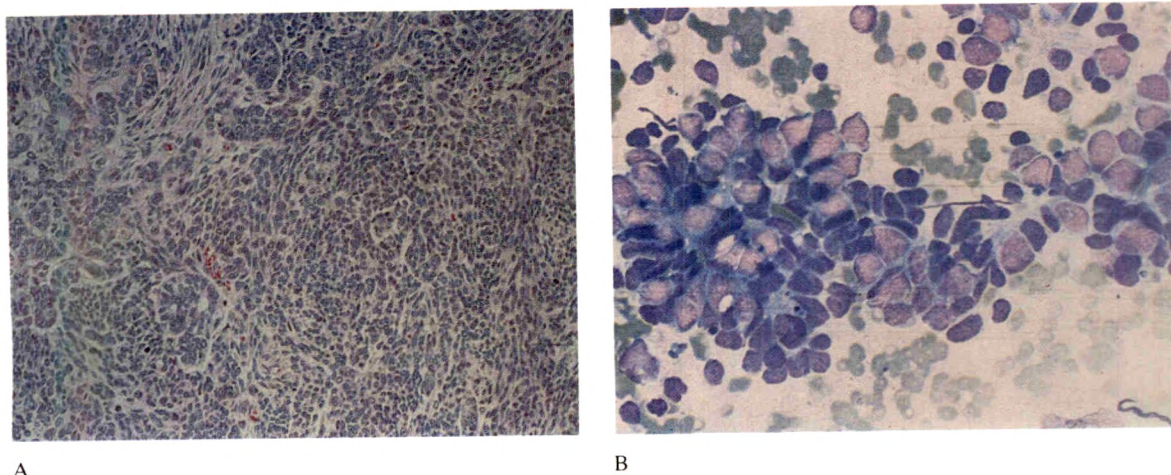


B



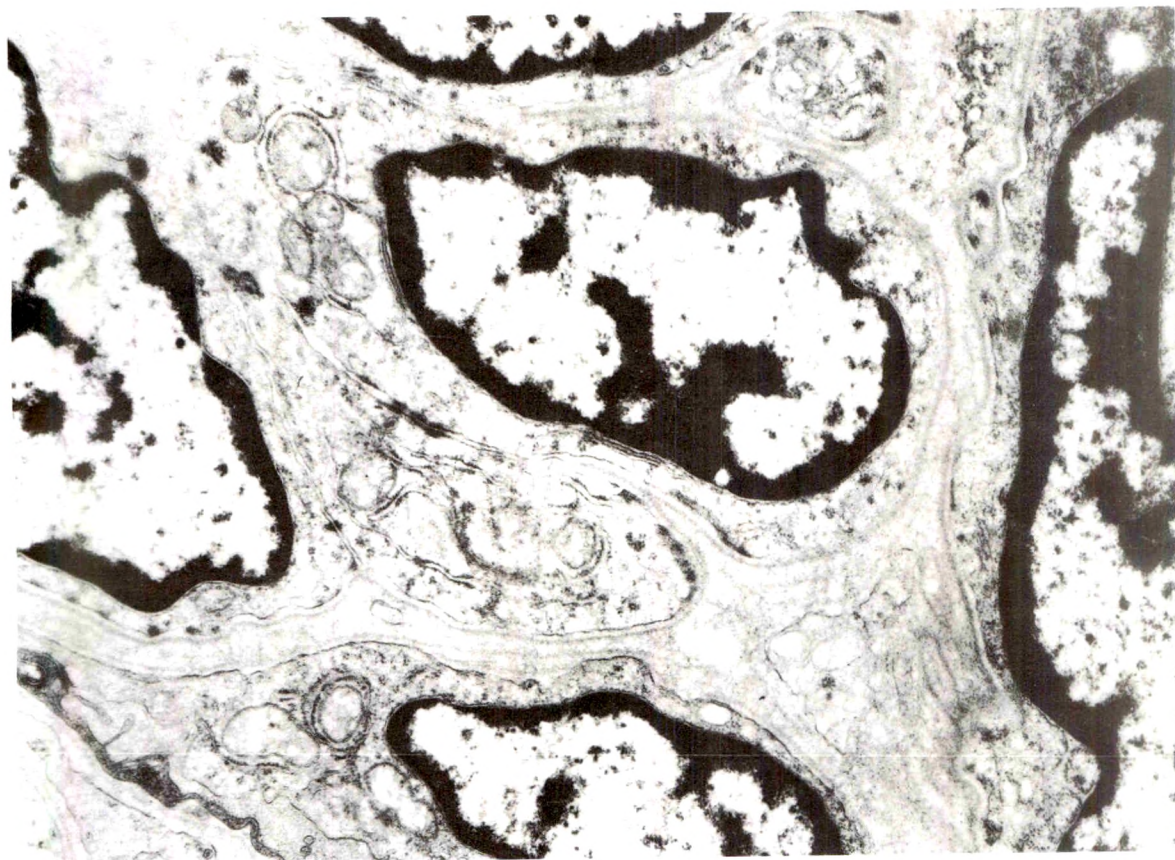
C

FIGURE 4. (A) Histopathological appearance of neuroblastoma featuring small round cells with abundant intercellular fibrillar material. (Hematoxylin-eosin; original magnification, $\times 250$.) (B) Aspiration smear from neuroblastoma depicting small round cells with abundant eosinophilic intercellular material. (Diff-Quik; original magnification, $\times 250$.) (C) Electronmicrograph showing an area from neuroblastoma in which a tumor cell is associated with several cytoplasmic cell processes. Scattered neurosecretory granules are present within the cell process and the main cell body. (Uranyl acetate and lead citrate; original magnification, $\times 33000$.)



A

B



C

FIGURE 5. (A) Histological section from Wilms' tumor showing blastemal and epithelial components. (Hematoxylin-eosin; original magnification, $\times 200$.) (B) Aspiration smear showing large pale epithelial cells forming tubules intermixed with smaller cells with dense nuclei. (Diff-Quik; original magnification, $\times 200$.) (C) Electronmicrograph showing undifferentiated tumor cells forming tubules which are surrounded by basal lamina. Intercellular junctions are also seen. (Uranyl acetate and lead citrate; original magnification, $\times 14500$.)

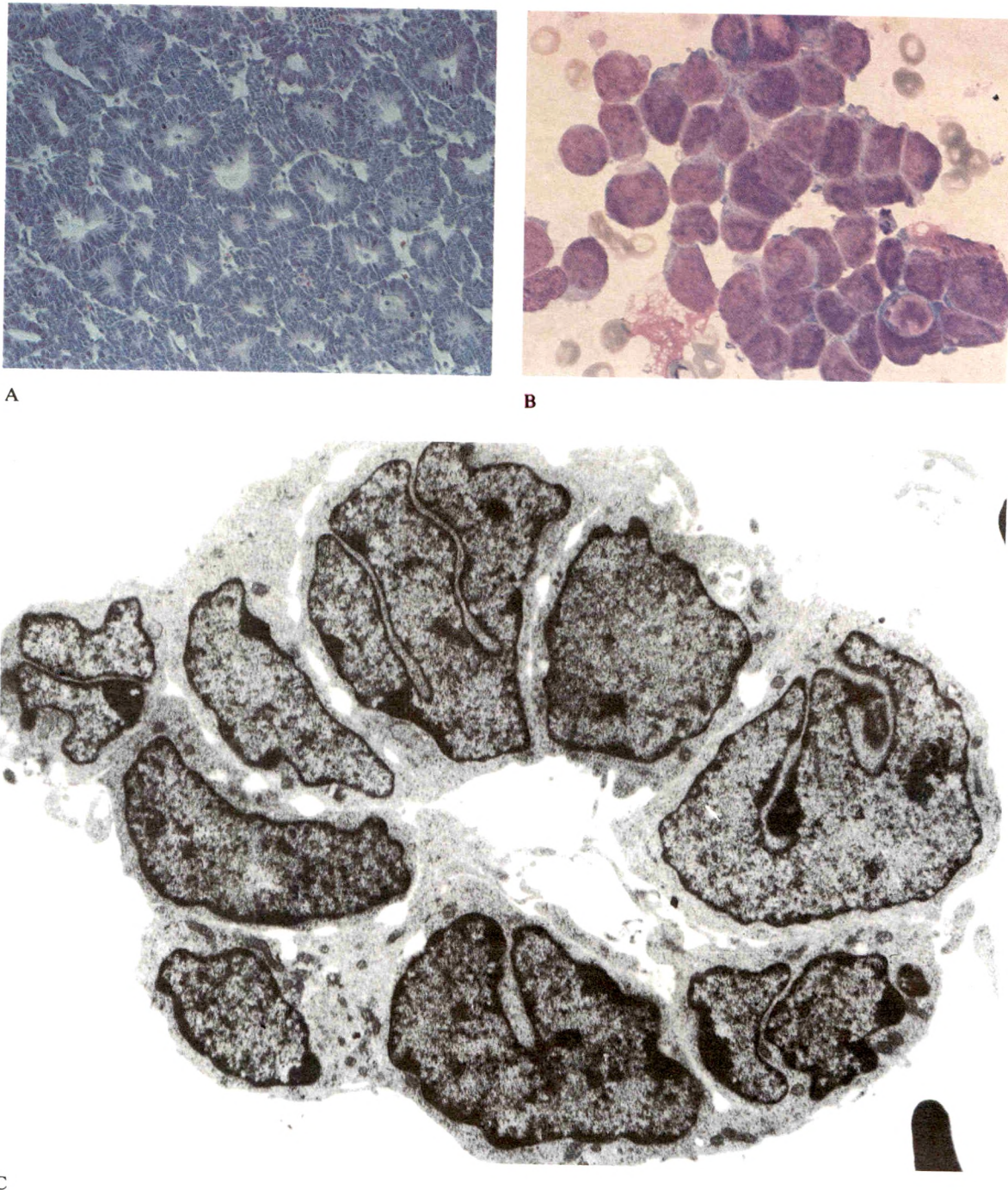


FIGURE 6. (A) Histological section from retinoblastoma featuring undifferentiated tumor cells and prominent rosette formation. (Hematoxylin-eosin; original magnification, $\times 250$.) (B) Aspiration smear from neuroblastoma showing small undifferentiated cells arranged in small clusters with rosette formation. (Diff-Quik; original magnification, $\times 300$.) (C) Electronmicrograph showing a cluster of tumor cells from retinoblastoma forming a rosette. Within the lumen of the rosette, a few small cytoplasmic cell processes are present. (Uranyl acetate and lead citrate; original magnification, $\times 6800$.)

ponding to rosettes are usually found in variable numbers (Figure 6B).

Ultrastructurally, the tumor cells are tightly arranged and show small amounts of cytoplasm in which mostly free ribosomes and occasional mitochondria are present. Rosettes are arranged in a circular fashion that enclose a lumen in which small cytoplasmic processes extend from surrounding tumor cells (Figure 6C). There are no neurosecretory granules or cytoplasmic intermediate filaments [6,19].

In addition to the round-cell malignant tumors described, a variety of other neoplasms and tumor-like conditions may be encountered in children. These include histiocytosis X, germ-cell tumors, sarcomas of bone and soft tissue, and tumors of the central nervous system. All these tumors may be diagnosed by FNAB [20-23].

Discussion

FNAB is now being used for diagnosing a large variety of neoplasms and inflammatory conditions. Aspiration biopsy has advantages over surgical biopsy because it is simple, relatively painless, and extremely cost effective. The procedure can be performed in an outpatient clinic and can be repeated as often as required. The results are usually available within a few minutes. In most patients, it ends the need for anesthesia and a surgical procedure. The results are usually reliable in the hands of pathologists who are experienced in performing the technique and interpreting the findings.

The use of FNAB in the diagnosis of childhood malignancies has been limited because most of the malignant neoplasms in children are the round cell type, such as malignant lymphoma, rhabdomyosarcoma, neuroblastoma, Ewing's sarcoma, Wilms' tumor, and retinoblastoma. A precise histological or cytological diagnosis in these cases may occasionally be difficult because these tumors are composed of small undifferentiated round cells which may not exhibit any distinctive morphological features when examined by light microscopy.

An important prerequisite for precise cytological diagnosis of childhood neoplasms is good-quality smears stained by an appropriate stain. In our laboratory, most of the FNAB smears are air-

dried and then stained by Diff-Quik. In many laboratories, the aspiration smears are fixed in alcohol and stained by Papanicolaou stain or hematoxylin-eosin. Although these staining procedures are more than adequate for FNAB diagnosis in general, we believe that Diff-Quik stain is the best for diagnosing childhood malignancies. It produces excellent details of cell cytoplasm and the intercellular matrix, which is extremely helpful in the diagnosis of childhood neoplasms.

During the first half of the study period, we attempted to confirm the cytological diagnosis of childhood malignancies by using additional techniques, such as preparing a cell block from the aspirated material or by processing part of the aspirate for immunohistochemical and electron microscopy studies. However, as the experience with these lesions increased, it was possible to make a confident diagnosis of many of these tumors based on FNAB cytology alone. Consequently, in recent years, the use of special techniques such as electron microscopy has been limited to a small proportion of cases in which the FNAB findings were equivocal or the clinical presentation of the tumor was unusual.

References

1. Tao LC, Pearson FG, Delarue NC, et al. Percutaneous fine-needle aspiration biopsy: its value to clinical practice. *Cancer* 1980;45:1480-5.
2. Orell SA, Sterrett GF, Walter MN, et al. Manual and atlas of fine-needle aspiration cytology. New York: Churchill Livingstone, 1986.
3. Frable WS. Fine needle aspiration biopsy: a review. *Human Pathol* 1983;14:9-28.
4. Koss LG. Thin-needle aspiration biopsy: past, present and future (editorial). *Acta Cytologica* 1980;24:1-3.
5. Schultenover SJ, Rawzy L, Page CP, et al. Needle aspiration biopsy: role and limitation in surgical pathology. *Am J Clin Pathol* 1984;82:405-10.
6. Akhtar M, Ali MA, Sabbah R, et al. Fine-needle aspiration biopsy diagnosis of round cell malignant tumors of childhood: a combined light and electronmicroscopic approach. *Cancer* 1985;55:1805-17.
7. Wakely P, Thomas F, Kardos MD, Frable WJ. Application of fine-needle aspiration biopsy to pediatrics. *Hum Pathol* 1988;19:1383-6.
8. Rajawanshi A, Rao KLN, Marwaha RK, et al. Role of fine-needle aspiration cytology in childhood malignancies. *Diagn Cytopathol* 1989;5:378-82.
9. Akhtar M, Ali MA, Huq M, Faulkner C. Fine-needle aspiration biopsy: comparison of cellular yield with or without aspiration. *Diagn Cytopathol* 1989;5:162-5.
10. Akhtar M, Bakry M, Nash EJ. An improved technique for processing aspiration biopsy for electron microscopy. *Am J Clin Pathol* 1986;85:57-60.

11. Akhtar M, Ali MA, Sabbah R. Aspiration cytology of Ewing's sarcoma: light and electron microscopic correlations. *Cancer* 1985;56:2051-60.
12. Jon ASH, Kessel VVN, Heerde PR. Fine-needle aspiration biopsy diagnosis of rhabdomyosarcoma: an immunohistochemical study. *Acta Cytol* 1987;31:573-77.
13. Seidal T, Walaas L, Kindblom LG, Angervall L. Cytology of embryonal rhabdomyosarcoma: a cytologic, light microscopic, electronmicroscopic and immunohistochemical study of seven cases. *Diagn Cytopathol* 1988;4:292-9.
14. Akhtar M, Ali MA, Sabbah R, et al. Fine-needle aspiration cytology of neuroblastoma: light and electron microscopic correlations. *Cancer* 1986;57:797-803.
15. Akhtar M, Ali MA, Sackey K, et al. Aspiration cytology of neuroblastoma: light microscopy with transmission and scanning electron microscopic correlations. *Diagn Cytopathol* 1988;4:323-7.
16. Silverman JF, Dehbe DJ, Ganick DJ, et al. Fine-needle aspiration cytology of neuroblastoma including peripheral neuroectodermal tumor with immunohistochemical and ultrastructural confirmation. *Acta Cytol* 1988;32:367-76.
17. Miller TR, Böttles K, Abele JS, Beckstead JH. Neuroblastoma diagnosed by fine-needle aspiration biopsy. *Acta Cytol* 1985;29:461-8.
18. Akhtar M, Ali MA, Sackey K, et al. Aspiration cytology of Wilms' tumor. *Diagn Cytopathol* 1989;5:269-74.
19. Akhtar MA, Ali MA, Sabbah R, et al. Aspiration cytology of retinoblastoma: light and electronmicroscopic correlations. *Diagn Cytopathol* 1985;4:306-11.
20. Layfield LJ, Anders KH, Glasgow BJ, Mirra JM. Fine-needle aspiration of primary soft tissue lesions. *Arch Pathol Lab Med* 1986;110:420-4.
21. Kindblom LG. Light and electron microscopic examination of embedded fine-needle aspiration biopsy specimens in pre-operative diagnosis of soft tissue and bone tumors. *Cancer* 1983;51:2264-77.
22. Akhtar M, Ali MA, Sackey K, et al. Fine-needle aspiration biopsy (FNAB) diagnosis of endodermal sinus tumor: histologic and ultrastructural correlations. *Diagn Cytopathol* (in press).
23. Akhtar M, Ali MA, Haq M, Bakry M. Fine-needle aspiration biopsy of seminoma and dysgerminoma: cytologic, histologic and electron microscopic correlations. *Diagn Cytopathol* 1990;6:99-105.

FISTULA-IN-ANO: A PATHOLOGICAL STUDY

Jehoram T. Anim, FRCPATH; Saleh A. Sowayan, DABPATH;
Chris S. Grant, FRCS; Hassan Al-Breiki, Facharzt

أظهرت مراجعة لـ ٢٢٩ حالة ناسور شرجي في مستشفانا وجود نسيج التهابي لانوعي يبطن غالبية المسالك. كانت البطانة الظهارية موجودة لدى ٥٠ مريضا، وقد عثر عليها بنسبة أكبر لدى من هم دون العاشرة، الأمر الذي يدعم فكرة الأصل الولادي إلى جانب خمج الغدد الشرجية كما أشار آخرون إلى ذلك سابقا. هذا وقد يكون لمحتويات الأمعاء دور في استجابة الجسم الغريب التي شوهدت لدى العديد من المرضى. ولا يبدو للأمراض الخمجية المتوطنة دور في إحداث الناسور الشرجي.

A review of 229 cases of fistula-in-ano in our institution has shown that nonspecific inflammatory tissue lines the majority of tracts. Epithelial lining was present in 50 cases and was encountered proportionately more frequently in subjects under 10 years of age, thus supporting a congenital origin as well as infection of anal glands, earlier proposed by other workers. Intestinal contents may have a role in the foreign body response seen in many cases. Locally endemic infectious conditions do not appear to play a significant role in the cause of the disease.

Fistula-in-ano (FIA) is a disease that has been recognized since early times, but in spite of detailed early descriptions, our understanding of its pathogenesis is still unclear. The current consensus of an underlying infection of anal glands was first proposed by Herman and Desfosses in 1880 [1], and subsequently reinforced by other workers [2-4]. Since then, various clinicopathological aspects of the disease have been studied [5-8].

A review of local Arab medical literature has yielded only a few reports on FIA, most clinical, with emphasis on management [9-11]. This paper is a review of all cases seen in the pathology department of our hospital.

Material and Methods

All surgical specimens of FIA submitted to the pathology department of King Fahd Hospital of the University, Al-Khobar (KFHU), over the five-year period January 1984 to December 1988, were included in the study. The age and sex of the

patients were obtained from the request forms. Hematoxylin and eosin slides were reviewed by two pathologists. Available special stains reviewed included: Ziehl-Neelsen stain, periodic acid-Schiff reaction, and Gram and Giemsa stains. Histological parameters examined included the presence and type of epithelium lining the fistulous tract, the type of the inflammatory response, granuloma formation, and presence of a foreign body. Organisms specifically looked for were: acid-fast bacilli, fungi, *Schistosoma* ova, and *Leishmania* organisms. No attempt was made to quantitate the histological features, although their interrelationships and possible relationship to pathogenesis were observed.

Results

A total of 248 FIA specimens were seen in our laboratory during the five-year period. Nineteen specimens were adjudged unrepresentative and excluded from further study. Table 1 summarizes the age distribution of the remaining 229 FIA cases and shows a peak incidence in the fourth decade. There were 209 (91.3%) males versus 20 (8.7%) females, yielding a sex ratio of 10.5 males to 1 female.

Partial or complete epithelial lining of the tract

From the King Fahd Hospital of the University, Al-Khobar.

Address reprint requests and correspondence to Dr. Anim: College of Medicine, King Faisal University, P.O. Box 2114, Dammam 31451, Saudi Arabia.

Accepted for publication 23 June 1990.

was observed in 50 cases (21.8%). Columnar epithelium similar to that lining the anal glands was the most common (Table 2), indicating the involvement of anal glands in the formation of FIA. Squamous epithelial lining, in combination with columnar, was found in the depths of the FIA

TABLE 1. Age incidence of 229 cases of fistula-in-ano.

Age groups (yr)	Number	Percentage
0-9	9	3.9
10-19	7	3.1
20-29	57	24.9
30-39	91	39.7
40-49	39	17.0
50-59	19	8.3
60-69	1	0.4
70-79	2	0.9
Age not stated	4	1.8
Total	229	100

TABLE 2. Types of epithelium lining fistulous tracts in 50 patients with fistula-in-ano.

Type of epithelium	Number
Squamous only	16
Columnar alone	21
Transitional alone	0
Squamous and columnar	10
Columnar and transitional	3
Squamous and transitional	0
Total	50

TABLE 3. Other histological features of fistula-in-ano in 229 patients.

Histological feature	Number
Granulation tissue	213
Abscess	13
Polymorphs without abscess	116
Lymphocyte predominance	60
Scar	221
Foreign body granuloma	32
Caseating granuloma	2
Numerous eosinophils	9
Lymphoid follicles with germinal centers	3
Vegetable material	6

in 10 of 50 cases (20%). Five of the 50 patients with epithelial lining were in the first decade of life. As only 4% of our patients were under 10 years of age, this shows a much higher frequency of epithelial lining of fistulous tracts in this age group (5/9), compared with other age groups. Table 3 summarizes other important histological findings in this study. Two cases showing granulomatous inflammation with caseation were diagnosed as tuberculous. No fungi, *Leishmania* organisms, or *Schistosoma* ova were identified in any of the tissues studied.

Discussion

None of the many pathogenetic mechanisms of FIA suggested by various workers have been able to explain all types of fistulae [12]. However, the generally accepted view is that the disease is due to an intersphincteric abscess originating in an anal duct [3,13,14]. The reported nonspecific inflammatory tissue lining of the majority of fistulae [15] was confirmed in our study. Thus, we have demonstrated granulation tissue and surrounding scar tissue in 213 and 221 cases, respectively, emphasizing the chronicity of the disease. The presence of polymorphonuclear leukocytes in 116 cases, however, indicates continued activity of the inflammatory process, but frank suppuration or an abscess was seen in only 13 cases. The presence of an abscess has been reported more frequently by other workers [16], leading to the conclusion by some that the abscess is an antecedent of FIA [2,13,17].

The presence of anal gland epithelium lining the tracts in 50 patients (21.8%) in areas of intense inflammation confirms involvement of the anal glands in the formation of FIA. Squamous epithelium in the depths of FIA may be due to metaplasia of the usual columnar epithelium. Congenital abnormalities of anal glands with superimposed infection, as proposed by Parks [3], is supported by Fitzgerald et al [1], and also by our demonstration of a higher proportion of children under 10 years of age (5/9) with epithelial lining of FIA in this study. Repeated or chronic inflammation and scarring may also be responsible for loss of epithelial lining with time, hence its relative infrequency in older age groups as seen in this study.

Foreign body granulomata were identified in 32 cases, and six constituted a reaction to vegetable material from intestinal contents. Although no foreign body could be demonstrated in the remaining 26, the granulomatous response in these may also be due to intestinal contents. However, other causes of granulomatous inflammation, including inflammatory bowel disease, cannot always be excluded [18,19]. Entry of fecal material into anal glands may thus be an important factor in the genesis of FIA. In two other cases, the granulomatous response showed typical caseation, consistent with tuberculous infection. Although tuberculosis is common in parts of Saudi Arabia, this represents only 0.9% of the cases studied, a figure similar to that reported in the United Kingdom by Marks et al [8] who found a decrease in the incidence of tuberculosis as a cause of anal fistula from 16% to less than 1% at St. Mark's Hospital (London) over a 50-year period.

FIA due to actinomycosis has been described by Fry et al [21]. However, no fungal elements were demonstrated in any of our cases. *Schistosoma mansoni* is endemic in parts of Saudi Arabia, but no ova or other evidence of *Schistosoma* involvement in FIA was demonstrated in this study. Similarly, no leishmanial organisms were present in any of the FIA studied. These negative findings suggest that locally endemic or common infectious agents may not be significantly implicated in the inflammatory process of FIA.

Nearly two-thirds (64.6%) of all cases in this study occurred in the third and fourth decades, thus emphasizing that it is a disease of young adults. This agrees with the findings of other workers [16,22,23] and also supports the suggestion that the disease process starts in the young, coming to light in early adulthood, following repeated infections. It is uncommon after the age of 60, as shown in Table 1. The sex ratio in our study confirms the male predominance of the disease, as reported by many workers [16,24-25], who have quoted ratios of approximately 2 to 3 males to 1 female. However, our ratio of 10.5 to 1 is far in excess of the findings of these workers. Reasons for this distribution in our study are not apparent, although in his discussion of the late presentation of breast cancer in Saudi Arabia, Sebai [27] theorized that Saudi women may not readily seek medical help on account of shyness.

Acknowledgment

We wish to thank Miss Juliet David of the Department of Pathology, KFHU, for invaluable clerical and technical assistance.

References

1. Fitzgerald RJ, Harding B, Ryan W. Fistula-in-ano in childhood: a congenital etiology. *J Pediatr Surg* 1985;20:80-1.
2. Eisenhammer S. Internal anal sphincter and anorectal abscess. *Surg Gynecol Obstet* 1956;103:501-6.
3. Parks AG. Pathogenesis and treatment of fistula-in-ano. *Br Med J* 1961;5224:463-9.
4. Harkins HN. Correlation of the newer knowledge of surgical anatomy of the anorectum. *Dis Colon Rectum* 1965;8:154-7.
5. Parks AG, Stitz RW. The treatment of high fistula-in-ano. *Dis Colon Rectum* 1976;19:487-99.
6. Goldberg SM, Parks AG, Goligher JC, et al. Fistula-in-ano. *Dis Colon Rectum* 1976;19:487-528.
7. Parks AG, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. *Br J Surg* 1976;63:1-12.
8. Marks CG, Ritchie JK. Anal fistulas at St. Mark's Hospital. *Br J Surg* 1977;64:84-91.
9. Jamjoom AMR. Fistula-in-ano: a one-day surgical approach and treatment for fistula-in-ano. Presented in Proceedings of the Fifth Saudi Medical Meeting, Riyadh, Saudi Arabia. 1980;609-18.
10. Al-Breiki H, Grant CS, Khawaja S, Wosornu L. Anal fissures, abscesses and fistulae. *Trop Doctor* 1985;15:108-10.
11. Fatayer WT. Outpatient proctology. *Jordan Med J* 1983;17:137-43.
12. Ferguson JA, Mackeigan JM. Haemorrhoids, fistulae and fissures: office and hospital management—a critical review. *Ad Surg* 1978;12:140-9.
13. Lilius HG. Fistula-in-ano: an investigation of human foetal anal ducts and intramuscular glands and a clinical study of 150 patients. *Acta Chir Scand [Suppl]* 1968;383:1-88.
14. Parks AG, Morson BC. The pathogenesis of fistula-in-ano. *Proc R Soc Med* 1962;55:751-4.
15. Rosai J. Ackerman's Surgical Pathology, ed 6. New York: Mosby, 1987;560-651.
16. Ramanujam PS, Prasad ML, Abcarian H. Perianal abscess fistulas: a study of 1023 patients. *Dis Colon Rectum* 1984;27:593-7.
17. Hanley PH. Anorectal abscess fistula. *Surg Clin North Am* 1978;58:487-503.
18. Gray BK, Lockhart-Mummery HE, Morson BC. Crohn's disease of the anal region. *Gut* 1965;6:515-25.
19. Lennard-Jones JE, Lockhart-Mummery HE, Chir M, Morson BC. Clinical and pathological differentiation of Crohn's disease and proctocolitis. *Gastroenterology* 1968;54:1162-70.
20. Logan VS. Anorectal tuberculosis. *Proc R Soc Med* 1969;62:1227-30.
21. Fry GA, Martin WJ, Dearing WH, Culp CE. Primary actinomycosis of the rectum with multiple perianal fistulae. *Mayo Clin Proc* 1965;40:296-9.
22. Read DR, Abcarian HA. A prospective study of 474 patients with anorectal abscess. *Dis Colon Rectum* 1979;22:566-8.

23. Vasilevsky CA, Gordon PH. The incidence of recurrent abscesses of fistula-in-ano following anorectal suppuration. *Dis Colon Rectum* 1984;27:126-30.
24. Scoma JA, Salvati EP, Rubin RJ. Incidence of fistulas subsequent to anal abscesses. *Dis Colon Rectum* 1974;17:357-9.
25. Waggener HU. Immediate fistulotomy in treatment of perianal abscess. *Surg Clin North Am* 1969;49:1227-33.
26. Eisenhammer S. The anorectal fistulous abscess. *Dis Colon Rectum* 1966;9:91-106.
27. Sebai ZA. Cancer in Saudi Arabia. *Ann Saudi Med* 1989;9:55-63.

JEDDAH EXPERIENCE IN THE MANAGEMENT OF HIGH ANAL FISTULA

Adnan Mohamed Rashid Jamjoom, MD; Yasir Saleh Jamal, MD

عالجنا بنجاح على مدى ثلاث سنوات ستا وعشرين حالة من الناسور الشرجي خلال المصرة مختلطة بانتشارات عالية ثانوية وست عشرة حالة من الناسور الشرجي فوق المصرة مختلطة بانتشارات عالية ثانوية أيضاً. يعتمد أسلوب العملية على تقصي السطح الوسيط للمصرة وإزالة المصدر الأولي للالتهاب الجرثومي واستئصال المسلك الأولي، مع نزح الانتشار العالي الثانوي. توبعت حالة المرضى لمدة سنتين بدون معاودة للمرض. كانت نسبة ضبط الغازات والفضلات السائلة ٩٢,١٪ و ٩٦,١٥٪ على التوالي لمجموعة الناسور خلال المصرة ونسبة ٧٥٪ و ٩٣,٧٥٪ على التوالي لمجموعة الناسور فوق المصرة في حين أن نسبة ضبط الفضلات الصلبة بلغت نسبة ١٠٠٪ لكلتا المجموعتين. وبالتالي فإن ما ندعوه أسلوب الاستئصال في علاج الناسور العالي يعتبر آمناً ويحقق نتائج ممتازة.

Twenty-six (26) transsphincteric anal fistulae with secondary high extensions and sixteen (16) suprasphincteric anal fistulae with secondary high extensions have been treated successfully over a period of 3 years. The operative technique depends on exploration of the intersphincteric plane with removal of the primary source of the infection, together with excision of the primary tract, and drainage of the secondary high extensions. The patients have been followed for 2 years without recurrence. Continence for flatus and liquid feces was 92.1% and 96.15%, respectively, in the transsphincteric and 75% and 93.75%, respectively, in the suprasphincteric group but the continence for solid feces was 100% in both. Thus, the so-called excision technique for treatment of high fistula is safe and results are excellent.

Treatment of high anal fistula has been associated with the risk of incontinence, either partial or complete. The great Arabic philosopher and physician, Rhazes (Abu Baker Al-Razi 850-930 A.D.) [1] recommended incision for low anal fistula and the ligature method for high anal fistula. He was the first to warn of the risk of incontinence associated with the lay open method for treatment of high fistulae. Avicenna (Ibn Sina 980-1037 A.D.) [2], the famous Arabic physician, emphasized the risk of incontinence with the lay open method in high fistulae and advocated the ligature method. Abulcasis (Al-Zahrawi 936-1010 A.D.) [3] discouraged the treatment of high fistulae stressing the risk of incontinence.

To lay open a fistula without exact identification of the primary tract and its relation to the sphincteric muscles, is a dangerous procedure [4], as the laying open of transsphincteric running tract can lead to impaired continence particularly in elderly people who have weaker sphincters [5]. High fistula-in-ano is a real problem of considerable surgical importance. We have a large number of recurrent cases with persistent pain, recurrent abscesses, and distress related to being unclean for prayer referred to us. This paper describes our operative technique and reports our results.

Material and Methods

Between 1986 and 1989, 42 patients with high fistula-in-ano were treated at King Fahd Hospital and Al Shaty Hospital in Jeddah. The median age was 42 years (range 26 to 56). Twenty-six (23 males and 3 females) had transsphincteric and 16 (14 males and 2 females) suprasphincteric fistulae, both associated with high secondary extensions

From the Department of Surgery, King Abdul Aziz University Hospital, Jeddah.

Address reprint requests and correspondence to Dr. Jamjoom: King Abdul Aziz University Hospital, P.O. Box 6615, Jeddah 21452, Saudi Arabia.

Accepted for publication 17 December 1990.

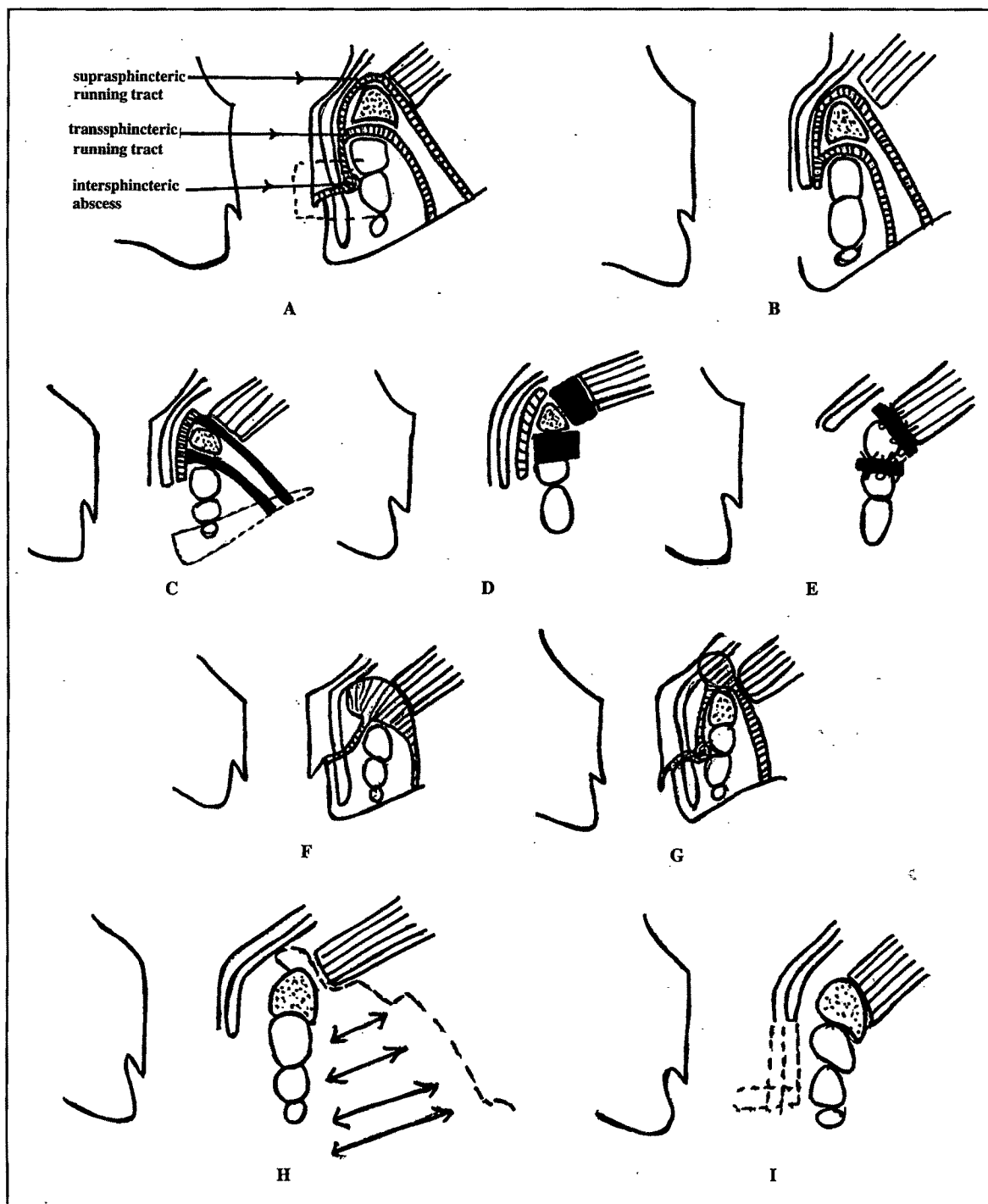


FIGURE 1. (A) Excision of mucocutaneous quadrant around the internal opening. (B) The intersphincteric plane is opened and explored. (C) Excision of the tracts in the ischiorectal fossa. (D) Post excision of the tracts and created muscle gap and adequate skin drainage. (E) Fistulotomy of the high intersphincteric tract and closure of the muscle gap. (F) Transsphincteric anal fistula with high blind tract which traverses the levator plate and opens into the abscess cavity (26 cases). (G) Suprasphincteric anal fistula with high tract which traverses the levator and opens into the abscess cavity (16 cases). (H) In all 42 cases, the high blind tracts which traverse the levator plate were found and opened into the chronic abscess cavity (Figure 1G and H). The tracts were curetted and adequately drained (Figure 1H). (I) Sliding flap of mucosa, submucosa, and circular muscle sutured to the level of dentate line.

penetrating the levator plate. All 42 patients had undergone previous surgery an average of 6 times for the transsphincteric group and 8 times for the suprasphincteric group.

Operative Technique

Following careful examination of the anorectum under general anesthesia with gentle probing and the injection of methylene blue, the fistula classification was determined and operation undertaken with three primary objectives [6,7]. First, to unroof the intersphincteric abscess in the anal canal by excising a piece of anodermal mucosa around the internal opening. The intersphincteric plane is then explored and exposed (Figures 1A and B). Infiltration with xylocaine 0.5% with adrenalin 1:400000 helps in providing an operative field with minimal bleeding which facilitates the exploration and dissection. Second, the primary tract is excised after inserting a probe through the external opening to the internal opening (Figure 1C). Further skin excision ensures adequate drainage (Figure 1D). The muscle gap created by excising the tract is sutured with dixon sutures (Figure 1E). The high intersphincteric tract is probed via the anal canal then fistulotomized by incising the mucosa and the internal sphincter (Figure 1E). Third, to drain the secondary high extensions in all cases, the high blind tracts which traverse the levator plate were found and opened into the chronic abscess cavity. The tracts were curetted and adequately drained (Figures 1F, G, and H). Then a sliding flap of mucosa, submucosa and circular muscle is mobilized and sutured to the level of the dentate line to cover the raw area of the muscle (Figure 1I), minimizing healing time and decreasing the risk of contamination.

Results

During the followup period all patients were asked about their ability to control flatus, liquid and solid stool and their answers were documented. The healing time was recorded and the patients were examined regularly for any recurrence up to 2 years postoperatively.

In the 26 patients with transsphincteric anal fistulae, the incidence of incontinence to flatus in the first 4 postoperative weeks was 50%. This

improved to involve only 2 cases (about 8%) after 24 weeks. A similar problem of incontinence to liquid stool was observed frequently in the first 4 weeks (50%), but improved significantly after 16 weeks to involve only one case (about 4%). With regard to solid stool, 2 patients were incontinent during the first 4 weeks, but after 8 weeks, all patients were continent (Table 1). No cases of recurrence were detected at the 2-year followup. The wounds took an average of 8 weeks to heal completely. In suprasphincteric anal fistulae (16 cases), very good results were achieved. Twelve patients (75%) were incontinent to flatus at 4 weeks postoperatively, 10 (about 62%) to liquid stool, and 5 (about 31%) to solid stool. This incontinence to flatus, liquid, and solid stool improved at 12 weeks to 50%, 25% and 12.5%, respectively, and improved further after 24 weeks to 25%, 6.25% and 0%, respectively (Table 2). Complete wound healing took an average of 10 weeks.

In all cases the results remained the same after the first 24 weeks until the end of the 2-year postoperative followup period.

TABLE 1. Results of the postoperative incontinence in transsphincteric anal fistulae (26 cases).

Time	Incontinence to		
	Flatus	Liquid	Solid
4 weeks	13 (50%)	3 (50%)	2 (7.69%)
8 weeks	8 (30.76%)	6 (23.07%)	0 (0%)
12 weeks	6 (23.07%)	4 (15.38%)	0 (0%)
16 weeks	4 (15.38%)	1 (3.85%)	0 (0%)
20 weeks	2 (7.69%)	1 (3.85%)	0 (0%)
24 weeks to 24 months	2 (7.69%)	1 (3.85%)	0 (0%)

TABLE 2. Results of postoperative incontinence in suprasphincteric anal fistulae (16 cases).

Time	Incontinence to		
	Flatus	Liquid	Solid
4 weeks	12 (75%)	10 (62.5%)	5 (31.25%)
8 weeks	10 (62.5%)	8 (50%)	4 (25%)
12 weeks	8 (50%)	4 (25%)	2 (12.5%)
16 weeks	6 (37.5%)	2 (12.5%)	1 (6.25%)
20 weeks	4 (25%)	1 (6.25%)	0 (0%)
24 weeks to 24 months	4 (25%)	1 (6.25%)	0 (0%)

Discussion

The management of high anal fistula is more complex than the low type because it carries the risk of incontinence and more liability to recurrence. In our experience the excision technique is a safe procedure for treatment of high anal fistulae, although it has the disadvantage of taking longer to heal as the surgically created wound is much larger than that produced by the lay open technique. But the quality of continence is much better and the recurrence rate certainly less. Kronberg [8] claimed in a randomized trial that the lay open operation was superior to excision, as it healed quickly and statistically the recurrence rate was not significantly higher than that which follows the excisional method, but the number of patients was relatively small (26 lay open and 21 excisions) and most of these cases were low fistulae. In contrast, Jones et al [9] describe a technique which is similar in principle to ours for high transsphincteric and suprasphincteric anal fistulae, in which the tract is cored out and the internal opening of the fistula is excised and then a rectal advancement flap is raised to cover the created raw area. Wedell et al [10] confirmed the efficacy of a similar technique for the treatment of high-level fistulae. The external wound is left open for drainage. The use of the rectal advancement flap and suturing of the muscle gap shorten the healing time and preserve the muscle complex. Reznick et al [11] described the technique of closure of the internal opening with rectal flap, wide external drainage and curettage of the tract. They reported excellent functional results.

Our results concerning incontinence, lack of recurrence and healing time are acceptable and comparable to other similar studies, in that we have no recurrences, the average healing time was 8 to 10 weeks and all patients were continent to solid stool. Stelzner [12] reported 141 cases of fistula-in-ano (73 intersphincteric and 68 transsphincteric and suprasphincteric) with sphincter weakness in 10% and a recurrence rate of 0.7%. Bennett [13] conducted a survey of 108 cases of anal fistulae. In 62% the fistulae were of the low anal type, with 38% trans- or suprasphincteric. The healing time of the fistulae varied according to the type. Five weeks was the average for low

anal fistulae and 14 weeks was the average for horse-shoe fistulae. Two cases of genuine recurrence were reported. In 6 other cases revision of the wound was necessary because of pus loculation. Twelve percent of the patients complained of occasional poor control of feces, 16% of imperfect control for flatus and 24% of frequent soiling of the underclothes.

Conclusions

The conservative operative management of high anal fistulae using the so-called excision technique is safe and the results are good. The other surgical alternatives for treatment of high anal fistulae have much higher rates of incontinence and recurrence. The exploration of the intersphincteric plane eliminates the source of infection and readily displays high extension which can be dealt with, preventing recurrence. The procedure is technically simple and recommended.

References

1. Abu Bakr Al Razi Zit. n. Stelzner (Rhazes). *Geschichte der Anorectalen Fisteln*, Springer-Verlag 1976.
2. Ibn Sina (Avicenna). *Alqanon Fi AlTEBB* (Second vol. p. 479-483).
3. Abulkasim Al-Zahrawi. (Abulcassis) Zit n. Stelzner. *Geschichte der anal fistel, Die anorectalen fisteln*, Springer-Verlag 1976.
4. Parks AG, Gordon PH, Hardcastle JD. Classification of fistula in ano. *Br J Surg* 1976;63:1-12.
5. Poos RJ, Frank J, Bitter R et al. Influence of age and sex on anal sphincters: manometric evaluation of anorectal continence. *Eur Surg Res* 1986;18:343-8.
6. Parks AG. Pathogenesis and treatment of fistula in ano. *Br Med J* 1961;463-9.
7. Parks AG, Stitz RW. Treatment of high fistula in ano. *Dis Col Rec* 1976;19:487-9.
8. Kronberg O. To lay open or excise a fistula in ano: a randomized trial. *Br J Surg* 1985;72:972.
9. Jones IT, Fazio VW, Jagelman DG. The use of transanal rectal advancement flaps in the management of fistulas involving the ano rectum. *Dis Col Rec* 1987;30(12):919-23.
10. Wedell J, Meier ZN, Eissen P, et al. Sliding flap advancement for the treatment of high level fistula. *Br J Surg* 1987;74:390-1.
11. Reznick RK, Bailey R. Closure of the internal opening for treatment of complex fistula in ano. *Dis Col Rec* 1988;31:116-8.
12. Stelzner R. Ergebnisse bei radikaloperationen von 141 analfisteln. *Chirurg* 1956;27:158.
13. Bennett RC. A review of the results of orthodox treatment for anal fistulae. *Proc Roy Soc Med* 1962;55:758.

THE MANAGEMENT OF ANORECTAL ABSCESS: AN INEXPENSIVE AND SIMPLE ALTERNATIVE TECHNIQUE TO INCISION AND "DEROOFFING"

William H. Isbister, MD; Stephen Kyle, MB

تم تدبير جميع المرضى المصابين بخراج شرجي مستقيمي الذين أحيلوا إلى قسم الجراحة في جامعة ولنتون منذ عام ١٩٨١م بالتزح المبسط بطريقة "DE PEZZER". تراوح قطر القنطرة المستخدم بين ٣ و ٥ ملم وكان يثبت عادة بالتبنيج الموضعي. نصف هنا بالتفصيل هذه الطريقة. بلغ عدد المراجعين المصابين بخراج شرجي مستقيمي ١٥٧ مريضاً، وبعد استثناء المصابين بخراج داخل المصرة، عولج مئة وأربعون مريضاً بالتزح بطريقة "DE PEZZER". كانت نسبة الذكور إلى الإناث ١:٢,٧. وكان مئة وعشرون مريضاً يعانون من خراج حول الشراج. تطلبت حالة ثلاثة وعشرون مريضاً تبنيجاً عاماً، أدخل عشرون منهم إلى المستشفى من بينهم ثلاثة عشر بسبب مشكلات طبية أساسية، كان ثلاثة منهم يعانون من داء كرون وخمسة من داء السكري. استمرت الأعراض لدى أربع وسبعين مريضاً لمدة أربعة أيام أو أقل وكان أربعون مريضاً يستخدمون مضادات حيوية موصوفة من قبل أطباء عامين. ولم تشر القصة المرضية لدى مئة وأربعة مرضى إلى إلتان شرجي مستقيمي سابق. تم نزع أربع وتسعين قنطرة في أقل من ١٥ يوماً. ومن بين المرضى الذين أجري لهم التزح تحت التبنيج الموضعي فقط، شكاً ثمانية من أن الألم لا يطاق إلى درجة تجعلهم يفضلون التبنيج العام في المستقبل. عاد ٥٣ مريضاً إلى ممارسة فعاليتهم وأعمالهم المعتادة خلال خمسة أيام بينما احتاج مئة وسبع مرضى إلى أربعة عشر يوماً قبل العودة إلى أعمالهم. ولم يكن نزح ثلاثة من الخراجات كافياً. نشأت نواسير لدى ٣٧ مريضاً خلال فترة المتابعة. يبدو أن طريقة النزح هذه آمنة وموثوقة وتحملها المرضى بشكل جيد ومن نتائجها تقصير فترة المكوث في المستشفى والعودة باكراً إلى العمل.

All patients with anorectal abscess who were referred to the University Department of Surgery in Wellington have been managed by simple "de Pezzer" drainage since 1981. The catheter used was between 3 to 5 mm in diameter and was usually inserted under a local anesthetic. The method is described in detail. One hundred and fifty-seven patients have presented with anorectal abscess, and after exclusion of those patients with intersphincteric abscess, 140 have been managed using de Pezzer drainage. The male to female ratio was 2.7:1. A perianal abscess was present in 120 patients. General anesthesia was necessary in 23 patients, and 20 of these patients were admitted to the hospital. Thirteen patients were admitted for underlying medical problems. Three patients had Crohn's disease and five were diabetics. Seventy-four of the patients had symptoms that had lasted for 4 days or less, and 40 patients had antibiotics prescribed by their local practitioners. There was no past history of anorectal sepsis in 104 patients. Ninety-four of the catheters were removed in less than 15 days. Of the patients who were drained under local anesthetic only, eight said that the pain was so "intolerable" that they would opt for a general anesthesia in the future. Fifty-three patients returned to their normal activities or work within five days, and 107 were back at work 14 days after drainage. Three abscesses were inadequately drained. Fistulae developed in 37 patients within the follow-up period. The technique appears to be safe and reliable, is well tolerated by patients, and results in minimal hospitalization and an early return to work.

From the Departments of Surgery, Wellington School of Medicine (Dr. Kyle), Wellington, New Zealand, and King Faisal Specialist Hospital and Research Centre (Dr. Isbister), Riyadh.

Address reprint requests and correspondence to Dr. Isbister: Department of Surgery, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

Accepted for publication 4 September 1990.

Anorectal sepsis may arise from infection in either skin structures (i.e., hair follicles, sweat glands, sebaceous glands) or the anal glands themselves (i.e., cryptoglandular disease). If a cryptoglandular abscess is incised and retains its internal communication, a fistula-in-ano results. Over-aggressive management of fistula-in-ano may result in incapacitating anal incontinence. It is our view that over-aggressive management of the initial sepsis may result in complex fistula formation and subsequently difficult fistula surgery. The danger to the mechanisms of continence in this event are obvious.

The true incidence of complicated fistula-in-ano, and postoperative incontinence in the Kingdom of Saudi Arabia is unknown, but a larger number of complicated fistulae-in-ano have been seen during three months in the Kingdom (W.N.I.) than were encountered during the entire period of the study reported in this paper. This impression is confirmed by a report from Jeddah [1] of 200 cases of "recurrent fistula in ano" in which 139 were intersphincteric, 40 were trans-sphincteric and 21 (10.5%) were suprasphincteric or "high fistulae."

The technique of de Pezzer catheter drainage of anorectal abscess was first described by Stuart in 1972 [2]. Since March 1981, we have used the method for all patients presenting with anorectal abscess to the University Department of Surgery in Wellington. In 1987 we reported our results with the technique in our first 97 patients presenting with anorectal abscess [3]. In this paper, we describe the technique in detail and update our results.

Material and Methods

Technique of Catheter Drainage

Insertion of the catheter is usually performed under local anesthesia although some patients request a general anesthetic.

With the patient in the left lateral position, and after administration of 10 mg of diazepam, a local anesthetic is injected into the skin overlying the point of maximum softening or fluctuation of the abscess (Figure 1). A small stab incision is made in the skin (3–4 mm in length) which must be just large enough to admit the cut-off mushroom of a self-retaining De Pezzer catheter (Figures 2, 3). The catheter is prepared by amputating the tip of

the catheter through the side holes so that a funnel-shaped catheter results. This is folded and grasped in a small hemostat prior to insertion through the stab incision into the abscess cavity itself (Figure 4). The excess catheter is cut off so that only 10 mm protrudes above the skin surface (Figure 5). A dry dressing is applied to the perineum overlying the catheter and the patient is

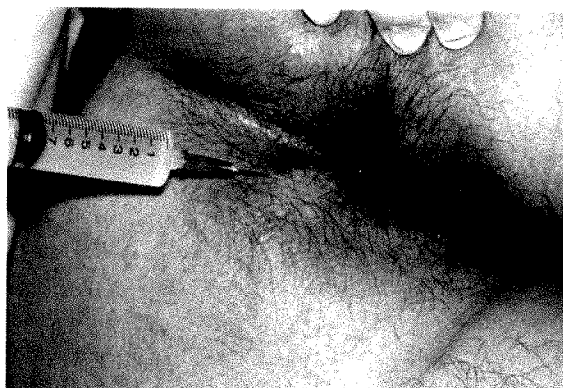


FIGURE 1. Injection of local anesthetic.

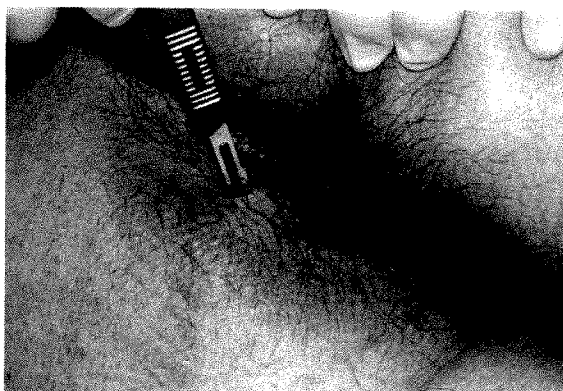


FIGURE 2. Stab incision at site of maximum fluctuation.



FIGURE 3. Pus draining from stab site before drain inserted.



FIGURE 4. "Cut off" catheter in hemostat about to be inserted into abscess cavity through stab incision.

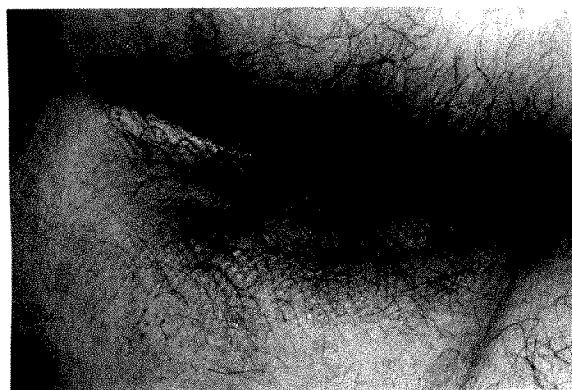


FIGURE 5. "Cut off" catheter in situ prior to dressing.

allowed to go home. Dressings are changed as necessary by the patient, the patient is reviewed after a week, and the catheter is removed at a second clinic visit a week later. Antibiotics are not administered and the patient's condition is reviewed a month following removal of the catheter. If drainage persists at this time, the patient is admitted to hospital for fistula surgery; otherwise, the patient is discharged.

Results

One hundred and fifty-seven patients with anorectal abscess have been treated by de Pezzer drainage in the 8 years between March 1981 and March 1989. Patient data were stored and analyzed on a microcomputer using software [4] written by one of the authors (W.H.I.).

Of the 157 patients analyzed, 17 were found to have intersphincteric abscess and these patients were generally managed by endoanal drainage (Table 1). Of the remaining 140 patients who form

the basis of this report, 102 were male and 38 were female, with mean ages of 39.7 and 39.5 years, respectively.

A perianal abscess was present in the majority of patients (Table 1), but in three the type of abscess could not be determined. Fifteen patients required no sedation. General anesthesia was necessary in 23 patients and 20 of these patients were admitted to the hospital (Table 2). Thirteen patients were admitted to the hospital because of underlying medical problems and ten were admitted because of sepsis (Table 2). No particular occupational groups seemed to be more prone to anorectal abscess (Table 3). The majority of patients did not have any predisposing or associated diseases (Table 4), although three patients had Crohn's disease and five were diabetic. There was a past history of anorectal sepsis in 36 patients (Table 5). Over half of the patients had symptoms which had lasted for four days or less (Table 6), and 40 patients had antibiotics prescribed by their local practitioners (Table 7). Ninety-four of the catheters were removed in less than 15 days (Table 8). No catheter was used in one patient with a superficial perianal abscess. There was no difference in the complication rate between the patients in whom the drain "fell out" before the first clinic visit, and those in whom the drain was retained and removed deliberately.

TABLE 1. *Type of abscess.*

Type of abscess	Number
Perianal	120
Ischiorectal	17
Intersphincteric	17
Indeterminate	3

TABLE 2. *Hospital admission.*

Hospital admission	Number
None (LA)	85
None (GA) immediate discharge	3
GA—1 day	12
GA—2 days	5
GA—≥ 3 days	3
Medical—1 day	8
Medical—2 days	2
Medical—≥ 3 days	3
For sedation recovery	9
For sepsis	10

GA = general anesthesia; LA = local anesthesia.

TABLE 3. *Patient occupation.*

Occupation	Number
Clerical	23
Professional	20
Retired	19
Manual worker	17
Housewife	17
Tradesperson	13
Skilled worker	13
Student	8
Salesperson	7
Other	3

TABLE 4. *Associated diseases.*

Associated disease	Number
None	110
Diabetes	5
Crohn's disease	3
Other (unrelated)	22

TABLE 5. *Previous anorectal sepsis.*

Previous sepsis	Number
None	104
Single abscess	15
2 abscesses	2
3 abscesses	2
> 3 abscesses	5
Previous fistula	5
Unknown	7

TABLE 6. *Duration of symptoms.*

Duration of symptoms	Number
< 25 hr	2
24-36 hr	3
36-48 hr	0
2 days	21
3 days	22
4 days	26
5 days	18
6 days	17
> 7 days	31

TABLE 7. *Use of antibiotics.*

Antibiotics	Number
None	85
Prescribed by general practitioner	40
Prescribed for patient toxicity	6
Prescribed for cellulitis	2
Other/unknown	7

TABLE 8. *Duration of catheterization.*

Catheter removal	Number
< 7 days (accident)	39
9 days	9
11 days	7
13 days	39
15 days	27
17 days	4
19 days	6
21 days	3
> 21 days	5
No catheter	1

Of the patients who were drained under local anesthetic, 34 were unable to remember the procedure, 32 claimed that the procedure was painless and acceptable, and 26 had slight pain but said they would have their abscess managed in the same way again. Eight felt that the procedure was very painful but would prefer drainage under local anesthetic to general anesthetic, and eight said that the pain was "intolerable" and would refuse drainage under local anesthesia in the future. No patient complained about the presence of a perineal drain during the study. Fifty-three patients returned to their normal activities or work within five days of drainage and 107 were back at work fourteen days after drainage.

Three abscesses were inadequately drained and were re-drained. Drainage continued after catheter removal, or further anorectal sepsis developed in 37 patients and these patients proceeded to fistula surgery. Follow-up varied from 12 months in the most recently drained patients to nine years in those patients treated during the first year of the study. Approximately 18 patients have been treated each year since the study commenced.

Patients who suffered "intolerable" pain during the procedure were compared with all other

TABLE 9. *Pain.*

	No pain (N = 109)	Pain (N = 8)	General anesthesia (N = 23)
Male: female ratio	2.9:1	1:1	2.8:1
Ischiorectal abscess	13/109 (11.9%)	0/8	4/23 (17.4%)
Subsequent fistula	24/109 (22.0%)	4/8 (50%)	9/23 (39%)

TABLE 10. *Subsequent fistula.*

	No fistula (N = 103)	Fistula (N = 37)
Male: female ratio	3.7:1	2.7:1
Catheter removal (< 14 days)	71/103 (68.9%)	23/37 (62.1%)
Intolerable pain	4/103 (3.9%)	4/37 (10.8%)
Previous anorectal sepsis	36/103 (34.9%)	16/37 (43.2%)
Need for general anesthesia	13/103 (12.6%)	10/37 (27%)

patients who claimed the procedure to be "painless," "slightly painful but would have again," or "can't remember" (Table 9). "Intolerable" pain seemed to be more common in young women and was associated with a higher incidence of subsequent fistula development.

Thirty-seven patients had fistulae develop following catheter drainage. Thirty-five of these patients originally had a perianal abscess. There seemed to be an association between the development of fistula and "intolerable" pain and a past history of anorectal sepsis. Fistula occurrence was more common in women (Table 10).

The mean length of hospital stay was 0.57 days for abscess drainage and 3 days for laying open of fistula. Overall mean hospitalization, including time for fistula surgery, was 1.4 days.

Discussion

This simple technique is safe and reliable, is well tolerated by patients, and results in minimal hospitalization and an early return to work. An important aspect of the technique is that it provides immediate and continuing relief of symptoms. Pus is drained and skin closure is pre-

vented until deep healing has taken place [2]. As soon as drainage is established, tension within the abscess decreases and symptoms are almost instantaneously relieved. Stuart [2] stresses that when the abscess is loculated the deep loculi will usually drain into the one in which the catheter is situated and this view is supported by the present study. This aspect of management is important because no accidental damage can be caused by "breaking down" loculi or probing in inappropriate directions. It is our contention that complicated fistulae may result from the latter unnecessary activities. It has never been necessary to drain a second loculus. Definitive fistula surgery was only required in 26.43% (95% C.I. = 19.4% - 33.4%) of our patients, whereas in the 474 patients reported by Read and Abcarian [5], a fistulous opening was demonstrated in 34% (95% C.I. = 30% - 38%) of the patients. The difference in fistula rates just fails to reach significance, but as our numbers rise, the statistic improves! In further support of our thesis is the absence of any supralelevator abscesses of fistulae in our series, although one might expect at least seven in a series of this size based on previously reported data [6]. It may be that the dangers of injudicious probing of the apex of an abscess cavity with "a curved 6-inch hemostat," in spite of the author's claims of the safety of the procedure, have been underestimated. The "high fistula" rate in Saudi patients is also high [1], and it may be that it too represents an over enthusiastic approach to the original anorectal sepsis.

Stuart [2] describes "prolonged" catheter drainage of at least a month, but we have not found it necessary to retain the catheter for such a long period. No patient has needed fistula surgery if the catheter site was found to be completely healed six weeks after abscess drainage. Thirty-nine catheters were displaced accidentally because skin incisions were too large for the cut off catheter, but none needed to be replaced.

Only 13 patients who were able to work remained off work for longer than fourteen days, but we have found a reluctance among New Zealand patients to return to their normal occupations when they had the excuse of "a drain in situ"! It may be argued that the method is not acceptable by Saudis and other Muslims because of their religious obligations, but the technique has been

used on four occasions in the Kingdom (W.H.I.), and so far no such problems or criticisms have been encountered!

Operating room complications (1%) and post-operative complications (2%), although uncommon in Read and Abcarian's [5] series, were nonexistent in the present series. Read and Abcarian [5] concluded that their standardized method of treatment has proven to be safe and effective: the use of the operating room and regional anesthesia facilitating the establishment of adequate drainage, a beneficial by-product being the sparing of a second operation in 34% of patients in whom a fistula can be identified. In comparison with the present series, however, it could be argued that an avoidable average hospital stay of 5.7 days (1.4 days including stay for definitive fistula surgery in present study) and the not inconsequential hospital costs, a high incidence of supra levator fistulae, between 1 to 7 days packing, two or three weeks off work, and final wound healing at 4 to 12 weeks postoperatively compares somewhat unfavorably with the minimal hospitalization, lower persisting fistula rate, earlier return to work, and zero morbidity of the present series.

It is time to re-examine the traditional approach to the management of anorectal abscess which

involves the patient's emergency admission to hospital, general anesthesia, surgery in an operating theatre, and a period of hospital convalescence involving wound packing and delayed wound healing. It is suggested that the fundamental surgical principle of draining pus with the minimum of operative interference and tissue damage and the maintenance of adequate drainage by a self-retaining catheter is difficult to improve upon and is endorsed by the present study. The use of the technique in the Kingdom of Saudi Arabia may well result in lower rates of anorectal sepsis-related complicated disease.

References

1. Jamjoom AMR. Fistula in ano: a review of 200 cases, a retrospective study. *Ann Saudi Med* 1989;9:625s.
2. Stuart M. Prolonged catheter drainage of anorectal abscess as a preliminary to elective fistulotomy. *Med J Aust* 1972;1:817-8.
3. Isbister WH. A simple method for the management of anorectal abscess. *Aust NZ J Surg* 1987;57:771-4.
4. Isbister WH. Microcomputers in surgery: a data file and analysis programme. *Aust NZ J Surg* 1983;53:465-9.
5. Read DR, Abcarian H. A prospective study of 474 patients with anorectal abscess. *Dis Colon Rectum* 1979;22:566-8.
6. Goligher JC. *Surgery of the anus, rectum and colon*, ed 5. London: Bailliere Tindall, 1984.

PANCREATIC PSEUDOCYST: A REVIEW OF 5 YEARS' EXPERIENCE

Saleh Hamza Al-Sulaimani, MB BCh, MD, Facharzt;
Mohammed Khurshid Alam, MS, FRCS(Ed)

نراجع في هذه الدراسة تجربتنا في تدبير الكيسة المعثكلة الكاذبة على مدار خمس سنوات، حيث نصف فيها النمط السببي والمظهر السريري والطرق التشخيصية والتدابير العلاجية. شكل التهاب المعثكلة المراري السبب الرئيسي في سلسلتنا هذه، إذ كان مسؤولاً عن نسبة ٤٥٪ من الحالات. راجعت الغالبية العظمى من المرضى (٦٩٪) المستشفى بسبب التهاب المعثكلة الحاد ونشأت الكيسة الكاذبة في وقت لاحق أثناء مكوث المريض في المستشفى. علماً بأن ما نسبته ٢١٪ من المرضى راجعوا المستشفى ولديهم كيسة معثكلة كاذبة مصحوبة بألم بطني معاود. لم تكن هناك كتل مجسوسة لدى ٤٨٪ من المرضى. كان تخطيط الصدى والتصوير المقطعي بالحاسوب أفضل وسيلتين للاستقصاء، إذ أظهرتا التشخيص الصحيح في ٩٥٪ و ١٠٠٪ من الحالات على التوالي. تلاشت الكيسة الكاذبة تماماً لدى ٢٤٪ من المرضى. وتلقى المرضى الذين راجعوا المستشفى بسبب التهاب المعثكلة الحاد معالجة محافظة في بادئ الأمر وحتى نضوج الكيسة إلى حد يسمح بالتدخل الجراحي. أما الذين راجعوا المستشفى ولديهم كيسة مكتملة التشوُّف فقد أجريت لهم الجراحة في وقت مبكر، بعد فترة كان متوسطها ١٦,٥ يوماً. استعمل التزج الداخلي لدى ٥٢٪ من المرضى. كانت المضاعفات الرئيسية خمج الصدر في (٣١٪) و خمج الجرح في (٩,٥٪). وبلغ معدل الوفيات الإجمالي ٥٪.

This retrospective study reviews our five-year experience with the management of cases of pancreatic pseudocyst. The etiological pattern, clinical presentation, diagnostic methods, and therapeutic measures are described. Biliary pancreatitis was the leading cause in our series, accounting for 45% of the cases. The majority of patients (69%) presented with acute pancreatitis, and pseudocyst subsequently developed during hospitalization. Twenty-one percent presented with developed pancreatic pseudocyst associated with recurrent abdominal pain. No mass was palpable in 48% of the patients. Ultrasonography and computed tomographic (CT) scanning were the two most useful investigations, yielding correct diagnosis in 95% and 100% of the cases, respectively. The pseudocyst completely resolved in 24% of the patients. Patients who presented with acute pancreatitis were initially treated conservatively until the cyst was mature enough for surgical intervention. Those who presented with well-developed cysts were operated on much earlier, after a mean period of 16.5 days. Internal drainage was used in 52% of the patients. The main complications were chest infection (31%) and wound infection (9.5%). The overall mortality was 5%.

A pancreatic pseudocyst is an extravasated collection of exocrine pancreatic fluid surrounded by a wall of granulation tissue and characteristically lacking an epithelial lining [1]. It is a relatively rare disease entity but one which presents significant problems in both diagnosis and management

[2]. Its incidence among patients with pancreatitis has been reported to range from 1 to 5% [3,4]. Etiological facts that have been reported include alcoholism (65%), biliary disease (15%), and trauma (7%) [5]. These figures, however, reflect the high percentage of alcoholic pancreatitis seen in Western countries. In our society, where alcohol consumption is extremely rare and cholelithiasis is quite common [6], biliary pancreatitis is more common than the other forms of pancreatitis [7].

From the College of Medicine, King Saud University, Riyadh.

Address reprint requests and correspondence to: Dr. Alam:
Department of Surgery, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Accepted for publication 22 August 1990.

In the recent past, the number of cases of pancreatic pseudocyst reported in the literature has risen dramatically [8]. With the advent of ultrasonography and computed tomography (CT) as diagnostic tools, pancreatic pseudocyst is being diagnosed with greater ease and this may be partially responsible for the increase in its incidence [9]. These modern imaging techniques have also made it possible to study the natural history of the disease. The subsequent demonstration of sporadic remission of untreated pseudocyst by these techniques has generated more controversy concerning the timing and role of surgery [10]. Bradley et al [11], in an excellent study on the natural history of pancreatic pseudocyst, suggested a course of management and defined the role and timing of surgery. They demonstrated that up to 20% of the cases of pseudocyst can resolve spontaneously within the first six weeks of presentation. Delay beyond this period was found to lead to an increased complication rate and higher mortality. Bradley et al [11] recommended an expectant approach for 4 to 7 weeks, to allow for spontaneous resolution as well as to allow the pseudocyst to mature so that satisfactory internal drainage can be instituted [11]. Although this approach has been accepted as sound by most clinicians, it has also been criticized because it causes an unnecessary and expensive delay in those patients who present with mature pseudocyst [12]. Early internal drainage has been reported [9,13] and some surgeons advocate scheduling surgery as soon as the diagnosis is made and the patient has been adequately prepared [8,14].

The aim of this report is to review our experience in the diagnosis and management of pancreatic pseudocyst, particularly the timing for surgery, as well as to highlight the epidemiological aspects of this disease in our area.

Material and Methods

The hospital records of 42 patients with a diagnosis of pancreatic pseudocyst and treated at Riyadh Central Hospital and King Khalid University Hospital at Riyadh during 1984 to 1989 were retrospectively reviewed. Detailed clinical data, which included presenting features, initial investigations, specific diagnostic procedures, etiological considerations, and medical as well as surgical

management including outcome, were recorded and analyzed.

Results

The patient population consisted of 42 patients, including 25 (60%) Saudis and 17 (40%) non-Saudis. Age ranged from 7 to 70 years with a peak incidence of 38.4 years. There were 28 (67%) males (average age, 38.2 years; range, 7–65 years) and 14 (33%) females (average age, 38.8 years; range 20–70 years).

Biliary pancreatitis was the leading cause in 19 (45%) of the patients, followed by idiopathic pancreatitis, 12 (28%); traumatic pancreatitis, five (12%)—all cases of blunt abdominal trauma due to motor vehicle accidents; and alcoholic pancreatitis, three (7%) (Table 1). Other causes of pancreatitis included hyperlipidemia in one patient, postoperative in one patient, and chronic renal failure in another patient.

The most common presenting symptom was epigastric pain, seen in 40 patients (95%), followed by vomiting observed in 24 patients (57%). The other common presenting symptoms included epigastric mass (on admission) in nine patients (21%), fever in nine patients (21%), and jaundice in two patients (5%). Three patients presented with hypotension (blood pressure < 100 mm Hg). Abdominal mass was palpable in nine patients on admission, and eight of them had had recurrent abdominal pain starting 5 days to 6 months before admission. Palpable epigastric mass developed in thirteen patients during hospitalization. The average interval between the acute onset of pancreatitis and a clinically palpable pseudocyst in these patients was 8.9 days. No mass was palpable in the remaining 20 patients (48%). The serum amylase activity upon admission was greater than 1000 units in 24 patients, between 500 and 1000

TABLE 1. Common causes of pseudocyst in this study and comparison with other series.

Type of pancreatitis	Martin et al [16]	Bradley et al [11]	Belinkie et al [2]	O'Connor et al [15]	Present series
Alcoholic	41%	83%	86%	74%	7%
Biliary	25%	—	3.5%	7%	45%
Traumatic	14%	—	—	—	12%
Idiopathic	—	—	3.5%	—	28%

units in 12 patients, and less than 500 units in six patients. Because it is noninvasive and repeatable, ultrasonography was most helpful diagnostically. It was performed in all patients, with most having more than one examination. Ultrasonography detected pseudocyst in all but two patients (95%). In these two patients, examination was technically difficult due to associated ileus. CT scanning was carried out in 24 patients (57%) and demonstrated pseudocyst in all.

Endoscopic retrograde cholangiopancreatography (ERCP) was done in nine patients to establish the cause of the pancreatitis and the diagnosis of pseudocyst and its relationship with the pancreatic duct. ERCP demonstrated chronic pancreatitis in two patients, pseudocyst-duodenal fistula in one patient, and evidence of extrinsic pressure on the duct system and duodenum in five patients. Communication between the pseudocyst and pancreatic duct was not demonstrated in any patient. Two patients had Gastrografin (meglumine diatrizoate) studies to assess the duodenal obstruction, which showed moderate extrinsic pressure. One patient underwent an hepatico-iminodiacetic acid (HIDA) scan, which excluded biliary disease. Twenty-nine patients (69%) were categorized as having acute pancreatitis (Group A), as they had been asymptomatic. Acute relapsing pancreatitis was identified in all 11 patients (26%) (Group B), as they presented with an acute episode but had a history of similar symptoms. Chronic pancreatitis was diagnosed in two patients (5%) based on the presence of recurrent symptoms and characteristic ERCP findings, and these patients constituted Group C. Table 2 shows the treatment methods used in the three groups.

TABLE 2. Surgical/non-surgical treatment used in different groups.

Treatment	Group A: acute pancreatitis (N = 29) ^a	Group B: acute relapsing pancreatitis (N = 11) ^b	Group C: chronic pancreatitis (N = 2) ^c
Cystogastrostomy	12	4	—
Cystojejunostomy	5	1	—
Percutaneous drainage	3	1	—
Conservative	10	5	2

^aTwo lost to follow-up.

^bTwo refused operation; one lost to follow-up.

^cOne patient unfit for surgery.

The median interval between admission and surgery was 48 days in Group A patients. Most Group B patients presented with an abdominal mass, with an interval of 16.5 days between admission and surgical intervention. Twenty-two patients from these two groups combined were treated by internal drainage.

Cystogastrostomy was the most favored operation. Percutaneous drainage under ultrasound guidance was performed in four patients (10%), of whom only one had an infected pseudocyst. Pseudocyst-colic fistula subsequently developed in this particular patient, who later died. Two patients, one of whom had a previous cystogastrostomy which became blocked and caused pseudocyst recurrence, had a good outcome following percutaneous drainage. In the fourth patient, pseudocyst recurred after percutaneous drainage but the patient refused further treatment. Among the patients treated conservatively, three refused surgery and one was deemed a poor candidate for any surgical procedure. It could not be determined from the records whether percutaneous drainage was considered in this patient. Thirteen patients had evidence of pseudocyst resolution at the time of discharge, but only ten patients (24%) completed follow-up. Their pseudocyst was completely resolved.

Chest infection was the most common complication (31%), followed by wound infection (9.5%). Two patients died following pseudocyst drainage, for a mortality of 5%. Of these two patients, one suffered pseudocyst-colic fistula, which led to septicemia and death; the other died of chest complications and renal failure following surgery. No preoperative death was recorded.

Discussion

Although pancreatic pseudocyst is an uncommon but well-recognized complication of both acute and chronic pancreatitis, the pathogenesis appears to be different for the two forms of the disease [13]. In the context of acute pancreatitis, the pseudocyst results from a process of autodigestion with acute tissue necrosis accompanied by duct disruption and leakage of pancreatic juice into the peripancreatic tissue. In chronic pancreatitis, duct obstruction, superimposed acute pancreatitis, or both, may result in a

pseudocyst clinically difficult to distinguish from a pseudocyst of acute pancreatitis [17]. Although alcoholic pancreatitis is the most common cause of pseudocyst in the Western population [2,11,15,16], biliary pancreatitis was the leading cause in the present series. In 28% of the cases in this study, the cause could not be established. This is a high incidence of idiopathic pancreatitis as compared to that reported in other series [2,11,15,16]. One explanation for this may be that a history of alcohol intake was not divulged by some patients because of the stigma attached to alcohol use in our society. The possibility of anatomic variations such as pancreatic divisum was excluded by ERCP in some of these patients.

The diagnosis of pancreatic pseudocyst can be a challenging problem, as the history, clinical examination, and laboratory data are frequently nondiagnostic. Even the palpable mass can frequently be deceptive, as it is often not possible to distinguish a pancreatic inflammatory mass (phlegmon) from a true pseudocyst. Nevertheless, persistent midepigastric pain, leukocytosis, and prolonged hyperamylasemia with a palpable abdominal mass evolving during an acute attack should suggest a diagnosis to a discerning physician. The introduction of ultrasound scanning has almost entirely eliminated the problem of diagnosis of pancreatic pseudocyst, and through serial studies, helped determine the appropriate timing of elective operations [10,11]. Serial ultrasonography also assists in following the progress of pseudocysts. In this study, 95% of the pseudocysts were diagnosed by ultrasonography, and in 24% of the patients, complete resolution of the pseudocyst was observed by serial ultrasonography. We routinely do ultrasonographic examinations on the second day of admission to establish the cause of the pancreatitis and to identify possible pancreatic edema or peripancreatic fluid collection. If the patient's condition fails to improve, hyperamylasemia persists, or signs of sepsis develop, the ultrasonographic examination is repeated.

CT scan was 100% accurate in diagnosing pseudocyst in our experience. This is in close agreement with the experience of other authors [18]. However, because of its cost and the risk of radiation, it cannot be recommended for serial use in following the process of the pseudocyst.

The optimal management of uncomplicated

pseudocyst with a mature wall is internal drainage into the stomach, duodenum, or small bowel [11]. Traditionally this has meant waiting as long as 6 weeks after the diagnosis until the cyst wall is mature enough to allow internal drainage [2]. A mortality of up to 60% has been reported when internal drainage was attempted within 6 weeks, but this dropped to 9% after a 6-week wait [19]. We have followed this traditional advice in patients with acute cyst (Group A). The mean interval between admission and surgery was 48 days in these patients. A routine wait of 6 weeks in all patients, such as those who present with a mature cyst, is unnecessary [12]. Such patients (Group B) can be identified by a clinical history of recurrent abdominal symptoms, a palpable mass on admission, and a well-formed pseudocyst on ultrasonographic examination and CT scan. Characteristic CT findings in such patients have been described [1]. The mean interval between diagnosis and operation in these patients was 16.5 days.

When immediate operation is required because of one of the complications of pseudocyst, such as rupture, hemorrhage, infection, biliary or gastric outlet obstruction, or persisting pain, the wall of the cyst is often immature and external drainage is necessary [12,20]. The percutaneous transgastric approach has achieved good results in patients with complications such as persisting abdominal pain, fever, enlarging fluid collection, and gastric outlet obstructions [21]. No patient in the present series had operative external drainage. Four patients had percutaneous drainage, one of whom suffered a pseudocyst-colic fistula, which was probably due to enzymatic digestion of colon rather than to the procedure. Another patient out of the four who had percutaneous drainage, developed recurrent cyst.

References

1. Mullins RJ, Malangoni MA, Bergamini TM, et al. Controversies in the management of pancreatic pseudocyst. *Am J Surg* 1988;155:165-71.
2. Belinkie SA, Russel JC, Dentsch J, Becker DR. Pancreatic pseudocyst. *Am Surg* 1983;49:586-90.
3. Joyce LD, Toledo-Pereyra LH, Humphrey EW. Pancreatic pseudocyst: a clinical review. *Am Surg* 1979;45:453-61.
4. Sandy JT, Taylor RH, Christensen RM, et al. Pancreatic pseudocyst. *Am J Surg* 1981;141:574-6.

5. Kohler H, Schafmayer A, Ludtke FE, et al. Surgical treatment of pancreatic pseudocysts. *Br J Surg* 1987;74:813-5.
6. Al-Sulaimani SH, Alam MK, Sengupta H, Gurgis A. Incidence of cholelithiasis in patients attending King Abdulaziz University Hospital. *Saudi Med J* 1986;7:261-5.
7. Laajam MA. Acute pancreatitis: experience in a university hospital in Riyadh, Saudi Arabia. *Ann Saudi Med* 1990;10:140-4.
8. Shantney CH, Lillechei RC. Surgical treatment of pancreatic pseudocyst—analysis of 119 cases. *Ann Surg* 1979;189:386-94.
9. Crass RA, Way LW. Acute and chronic pancreatic pseudocysts are different. *Am J Surg* 1981;142:660-3.
10. Bradley EL III, Clements JL Jr. Spontaneous resolution of pancreatic pseudocyst. *Am J Surg* 1975;129:23-8.
11. Bradley EL III, Clements JL Jr, Gonzalez AC. The natural history of pancreatic pseudocysts: a unified concept of management. *Am J Surg* 1979;137:135-41.
12. Ephgrave K, Hunt JL. Presentation of pancreatic pseudocysts: implications for timing of surgical intervention. *Am J Surg* 1986;151:479-53.
13. Warsaw AL, Ratner DW. Timing of surgical drainage for pancreatic pseudocyst. *Ann Surg* 1985;202:720-4.
14. Grace RR, Jordan PH Jr. Unresolved problems of pancreatic pseudocysts. *Am Surg* 1976;184:16-21.
15. O'Connor M, Kolars J, Ansel H, et al. Pre-operative endoscopic retrograde cholangiopancreatography in the surgical management of pancreatic pseudocysts. *Am J Surg* 1986;151:18-24.
16. Martin EW, Catalano P, Cooperman M, et al. Surgical decision making in the treatment of pancreatic pseudocysts—internal versus external drainage. *Am J Surg* 1979;138:821-4.
17. McConnell DB, Gregory JR, Sasaki IM, Vetto RM. Pancreatic pseudocyst: *Am J Surg* 1982;143:599-601.
18. Maruotti RA, Spina GP, Zannini P, et al. Current management of pancreatic pseudocysts. *Int Surg* 1982;67:299-305.
19. Shetty AN. Pseudocyst of pancreas: an overview. *South Med J* 1980;73:1239-42.
20. Hunt JL, Ephgrave K. Emergency surgery for pancreatic pseudocysts. *South Med J* 1987;80:462-5.
21. Matzinger FRK, Chia-Sing H, Yee AC, Gray RR. Pancreatic pseudocysts drained through a percutaneous transgastric approach: further experience. *Radiology* 1988;167:431-4.

DAMAGE TO THE BILE DUCTS AT CHOLECYSTECTOMY

Tarek Said Malatani, FRCS(C)

تصف هذه المقالة حالات ستة مرضى تعرضوا لإصابات علاجية المنشأ في القناة الصفراوية خارج الكبد عقب استئصال المرارة الانتخابي. شخّصت جميع الحالات بعد العملية بثلاثة أسابيع إلى سنة. لم يجر تصوير للأوعية الصفراوية لأي من المرضى خلال العملية الأولى لاستئصال المرارة للكشف عن أي شذوذ أو انسداد ولادي في الشجرة الصفراوية. شملت العوامل التي يحتمل أنها ساهمت في حدوث هذه الإصابات، النزف أثناء الجراحة واستكشاف القناة الصفراوية العامة لدى المصابين باليرقان الانسدادي وسوء المساعدة الجراحية. لم يظهر أن للسمنة أية أهمية لأن المرضى الستة كانوا نحيلين. من الأفضل تدبير الإصابات علاجية المنشأ في القناة الصفراوية حين حدوث الإصابة خلال العملية الأولى. ولدى اكتشاف هذه الإصابات في مرحلة تالية للجراحة، فإن المفاغرة الكبدية العفجية / المرارية تعطي أفضل النتائج.

Six patients who incurred iatrogenic injury to the extrahepatic bile duct following elective cholecystectomy are described. All cases were diagnosed three weeks to one year after operation. In none of the patients was an operative cholangiogram performed during the original cholecystectomy to detect congenital biliary tree anomalies or obstruction. Possible risk factors contributing to such injuries were intraoperative bleeding, common bile duct exploration in patients with obstructive jaundice, and poor surgical assistance. Obesity was not found to be of significance since all six patients were thin. Iatrogenic bile duct injuries are best managed at the time of injury during the primary operation. When recognized later in the post-operative period, choledocho/hepaticojejunostomy gives the best result.

Cholecystectomy is the most commonly performed major abdominal operation in Saudi Arabia [1]. Accidental injury to the biliary tract is an infrequent complication of this operation, but when it occurs, it is always very serious and associated with some mortality and high morbidity. It has been called "the most catastrophic complication of a straightforward cholecystectomy" [2]. The incidence of such injuries ranges from 0.2 to 0.9% in patients undergoing cholecystectomy [3-5].

This paper attempts to identify some of the possible risk factors in order to help surgeons avoid accidental injury to the biliary tree at cholecystectomy. These risk factors are intraoperative bleeding, jaundice prior to surgery warranting common

bile duct exploration, and poor intraoperative assistance. The results of hepaticojejunostomy with and without sutureless jejunal mucosal grafting are also identified [6,7].

During a follow-up period of 15 to 28 months (mean, 20 months), recurrent symptoms and evidence of biliary strictures were recorded.

Patients, Methods, and Results

Since February 1988, six patients had been referred to Assir Central Hospital with iatrogenic biliary tract injury following elective cholecystectomy performed in different district general hospitals of the Assir region. All cases were diagnosed in the postoperative period, three weeks to one year following cholecystectomy. All original operations were performed by a consultant surgeon with poor intraoperative assistance. In none of the patients was an operative cholangiogram performed.

From the Department of Surgery, College of Medicine, King Saud University, Abha Branch, Abha.

Address reprint requests and correspondence to Dr. Malatani: P.O. Box 575, Abha, Saudi Arabia.

Accepted for publication 2 September 1990.

Liver function tests were assayed on the Hitachi 704 autoanalyzer. Alkaline phosphatase was assayed using the p-nitrophenyl phosphate method (normal range at 37°C, 98–279 U/L) adult. Bilirubin was assayed by the Jendrassik method (normal value, < 17 $\mu\text{mol/L}$ for the total, < 3.7 $\mu\text{mol/L}$ for the direct).

Details of the six patients are as follows:

Patient 1

Jaundice developed in a 32-year-old woman 14 days after cholecystectomy and she was diagnosed as having a "possible retained common bile duct stone." On referral she was found to have a temperature of 38.7°C and a total bilirubin content of 219 $\mu\text{mol/L}$; direct bilirubin was 123 $\mu\text{mol/L}$. Ultrasound showed dilatation of the intrahepatic biliary tree. She was treated for cholangitis. Percutaneous transhepatic cholangiogram performed after her fever subsided showed marked dilatation of intrahepatic radicals with nonvisualization of the common hepatic and common bile duct (Figure 1).

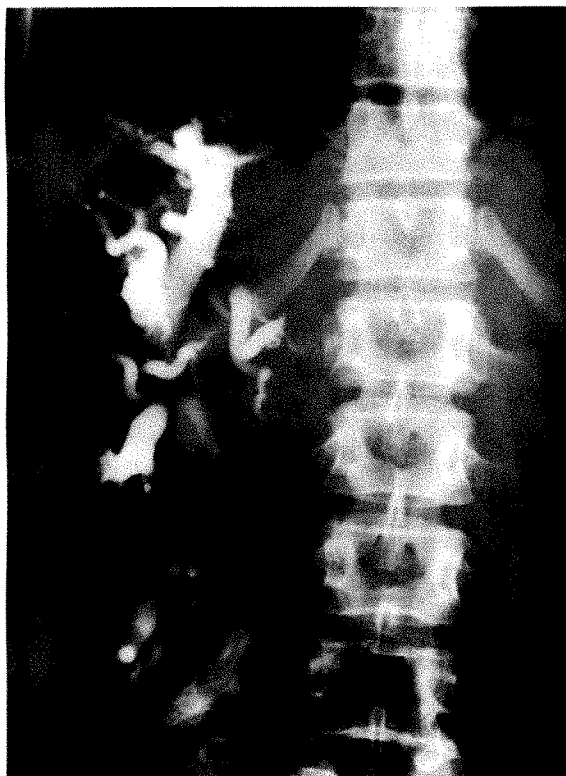


FIGURE 1. Marked dilatation of the right and left intrahepatic ducts with nonvisualization of the common hepatic and common bile ducts.

At exploration, silk stitches were found at the right and left hepatic ducts, deep in the porta hepatis. These stitches were removed and end-to-side sutureless mucosal, graft loop hepaticojejunostomy and enteroenterostomy were performed with two latex transhepatic stents, which were removed 6 weeks later. During a follow-up period of 28 months, she has had two readmissions for mild cholangitis which has been treated by systemic antibiotics and intravenous fluid therapy. Ultrasonography done on both occasions showed normal intrahepatic biliary ducts.

Patient 2

A 33-year-old woman was referred ten days after cholecystectomy; jaundice had developed three days before. Her total serum bilirubin was 209 $\mu\text{mol/L}$ and direct bilirubin was 116 $\mu\text{mol/L}$. Ultrasound showed a collection in the subhepatic area, which was confirmed by a computed tomographic scan. Patient refused a second operation and discharged herself from the hospital. Two weeks later, she was readmitted as an emergency case with massive ascites, normal temperature, and mild jaundice. Her total bilirubin concentration on this occasion was 65 $\mu\text{mol/L}$. Diagnostic paracentesis of the abdomen showed pure bile. At laparotomy a total of 13 liters of bile-stained ascites fluid was suctioned from the peritoneal cavity. A 1-cm-diameter hole with a friable edge was identified at the junction of the right and left hepatic ducts and a silk stitch was found below the hole in the common hepatic duct. Peritoneal lavage was performed and a Roux-en-Y, side-to-side sutureless jejunal mucosal graft hepaticojejunostomy was performed with two latex transhepatic stents. Both stents were removed after 6 weeks, and the patient made an uneventful recovery. She has remained well in a follow-up period of 27 months.

Patient 3

A 35-year-old woman underwent an elective cholecystectomy for symptomatic gall stones. On the sixth postoperative day she was noticed to have developed jaundice, which progressively increased. She was referred on the 25th day. Her total serum bilirubin content was 629 $\mu\text{mol/L}$, direct bilirubin was 274 $\mu\text{mol/L}$, and alkaline phosphatase was 684 U/L. Ultrasound showed

dilatation of the intrahepatic biliary ducts and the proximal part of the common hepatic duct. At reoperation, a single ligature around the distal portion of the common hepatic duct was found. This ligature was removed and proximal 2.5 cm of common hepatic duct was used to perform a Roux-en-Y hepaticojejunostomy with mucosa-to-mucosa sutures without a stent. The patient was free of symptoms and had a normal liver function test at 24 months' follow-up.

Patient 4

A 29-year-old woman developed jaundice 3 days after cholecystectomy. She was referred on the 14th postoperative day with a probable diagnosis of a retained common bile duct stone. On admission she had a total serum bilirubin level of 258 $\mu\text{mol/L}$; the direct bilirubin level was 150 $\mu\text{mol/L}$ and alkaline phosphatase activity was 1404 U/L. Ultrasonography showed dilated intrahepatic ducts, and percutaneous transhepatic

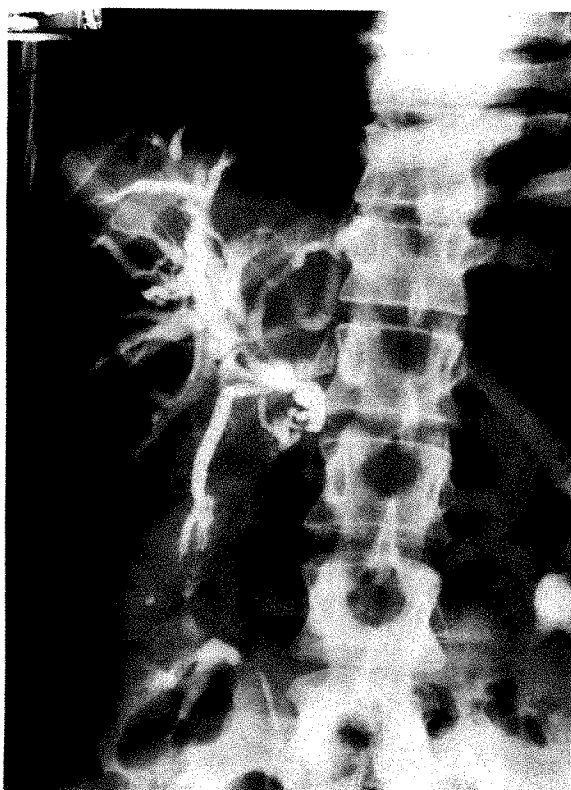


FIGURE 2. Moderate dilatation of the intrahepatic bile ducts with tight narrowing at the commencement of the common hepatic duct. A short distance distally there is complete obstruction of the common bile duct.

cholangiogram showed moderate dilatation of the intrahepatic bile ducts with a tight narrowing at the commencement of the common hepatic duct and complete obstruction of the common bile duct (Figure 2). At exploration, four silk sutures were removed from the region of the porta hepatis. A Roux-en-Y hepaticojejunostomy with mucosa-to-mucosa sutures was performed without stents. The patient remained symptom-free at 20 months' follow up.

Patient 5

A 48-year-old man underwent cholecystectomy and exploration of the common bile duct for gall stones and obstructive jaundice. At operation, multiple stones were removed from the common bile duct and a T-tube was placed in the choledochostomy. Four months prior to operation, he underwent gastric devascularization and esophageal transection/anastomosis for bleeding esophageal varices. T-tube cholangiogram was performed 6 weeks after cholecystectomy, and although the patient's jaundice had not abated, the T-tube was removed. One week later, the patient was referred to us with a serum bilirubin of 675 $\mu\text{mol/L}$ with a direct bilirubin of 311 $\mu\text{mol/L}$ and an alkaline phosphatase of 2585 U/L. Ultrasonography showed dilatation of the intrahepatic ducts.

A percutaneous transhepatic cholangiogram was performed that showed a block at the common hepatic duct and marked dilatation of the intrahepatic biliary tree. At laparotomy, Prolene stitches were identified at the porta hepatis and removed. Roux-en-Y hepaticojejunostomy was performed with mucosa-to-mucosa sutures, a T-tube was inserted through the wall of the Roux-en-Y loop, and a long arm was used to stent the anastomosis. During this operation, the cirrhotic liver bled from the gall bladder bed which was packed with Surgicel. In the immediate postoperative period, the drain in the subhepatic area drained frank blood and the patient underwent re-exploration. The bleeding from the liver bed was controlled by packs which were left in and removed 48 hours later in the intensive care unit. The patient made a satisfactory recovery. At 18 months follow up, he was asymptomatic with a total serum bilirubin of 30 $\mu\text{mol/L}$; direct bilirubin was 5 $\mu\text{mol/L}$.

Patient 6

A 45-year-old woman had undergone cholecystectomy one year before referral. One week after the operation, jaundice developed which was attributed to blood transfusion. She remained jaundiced for the whole year, when she was referred with a total serum bilirubin level of 118 $\mu\text{mol/L}$ and direct bilirubin of 50 $\mu\text{mol/L}$. Ultrasonography showed moderate dilatation of the intrahepatic bile ducts. At laparotomy, a silk stitch was identified at the porta hepatis and its removal demonstrated a stricture of the proximal common hepatic duct. A Roux-en-Y hepaticojejunostomy with sutureless mucosal graft over a Silastic transhepatic stent was performed. At 15 months follow up, she had normal liver function tests but she had been admitted twice during this period with mild attacks of cholangitis that responded to a short course of systemic antibiotics and fluid replacement therapy.

Follow-up for the six patients was carried out every three months by liver function tests and ultrasound which revealed no dilatation of the intrahepatic ducts even during the attacks of cholangitis in Patients 1 and 6 (Table 1).

Discussion

The single most important predisposing cause of bile duct injury in these six patients was bleeding at the time of cholecystectomy. This was established on retrospective inquiry from the surgeons. Injury to the bile ducts can occur even in the hands of experienced surgeons. In all our patients, lack of experience in dealing with the unexpected hemorrhage during cholecystectomy, particularly unfamiliarity with the Pringle's maneuver, resulted in indiscriminate application of sutures in the region of the porta hepatis.

Hemorrhage during cholecystectomy requires simple pressure for a few minutes followed by an adequate display of the bleeding source which allows safe management of the problem. Peroperative cholangiogram may also be used if blind stitches have been applied due to bleeding. The value of a properly performed peroperative cholangiogram before cholecystectomy cannot be overestimated. Cholecystectomy without a comprehensive picture of the biliary tree is like traveling in a strange countryside without a road map [8]. However, it is wrong to assume that operative

TABLE 1. *Summary of patient data.*

Patient no.	Age, sex	Total/direct bilirubin ($\mu\text{mol/L}$)	Interval between 1st & 2nd operation	Type of operation	Follow up (mo)	Complication
1	32,F	219/123	3 wk	Loop HJ with enteroenterostomy, sutureless, end-to-side transhepatic stents	28	Two attacks of mild cholangitis treated by antibiotics
2	33,F	209/116	5 wk	Roux-en-Y HJ, sutureless, side-to-side transhepatic stents	27	None
3	35,F	629/274	4 wk	Roux-en-Y HJ, side-to-side no stent	24	None
4	29,F	258/150 $\mu\text{mol/L}$	3 wk	Roux-en-Y HJ, side-to-side no stent	20	None
5	48,M	675/311 $\mu\text{mol/L}$	8 wk	Roux-en-Y HJ, side-to-side T-tube stent	18	None
6	45,F	118/50 $\mu\text{mol/L}$	1 yr	Roux-en-Y HJ, sutureless, end-to-side transhepatic stent	15	Two attacks of mild cholangitis treated by antibiotics

HJ = hepaticojejunostomy (all HJ are retrocolic); F = female; M = male.

cholangiography always affords protection against duct damage [9,10]. The injury can occur due to poor surgical technique after the study has shown a normal biliary tree, or because the operative cholangiogram was interpreted incorrectly [11]. Bengmark et al [11] reported 65 injuries of the choledochus at cholecystectomy in patients when peroperative cholangiography was performed in all except three. Surgeons performing cholecystectomy should be aware of the many anatomical variations which occur, especially in the Calot's triangle, and thus the need to expose the area clearly before any structures are divided, clamped, or ligated. Awareness of this fact could have prevented indiscriminate clamping of vessels when bleeding occurred intraoperatively in these six cases. The best time to repair the bile duct injuries is immediately when they are discovered during the primary operation. Therefore surgeons should be skilled enough to recognize and promptly repair the injury over a T-tube by end-to-end anastomosis, because it achieves the best results [12]. However, the choledocho/hepaticojejunostomy gives a better result when a segment of the bile duct is damaged, making tension-free end-to-end anastomosis technically difficult, or when the injury is diagnosed later in the postoperative period [13-15]. On inquiry it was also discovered that the surgeons who performed the six cholecystectomies were assisted by a very junior staff member or a nurse. Expert assistance could have avoided inadvertent injury.

Patient 5 in this study presented with jaundice before cholecystectomy. The surgeon had to explore the common bile duct, which subsequently resulted in its injury. It is therefore mandatory to investigate for precholecystectomy jaundice and common bile duct exploration when receiving these cases for management of possible iatrogenic injury to biliary tree, as common bile duct exploration is a considerable risk factor. The impression among surgeons is that obese patients are more prone to biliary tree injuries at cholecystectomy, because the operation is more difficult in obese than in thin patients. None of the six patients in this study was obese. Therefore this false sense of security in performing cholecystectomy in thin patients is highly undesirable.

Jejunal "mucosal graft" operation as described by Smith [16] was used in Patients 1, 2, and 6, and

was applied over a straight transhepatic latex rubber tube. It can be performed easily and avoids tedious dissection and difficult anastomosis, especially with friable tissues. The transhepatic stents were left in for 6 weeks, as there was no evidence that prolonged use of bile duct splint leads to better results than does use for 6 to 12 weeks [17-19].

We believe that use of the transhepatic tube, as originally described by Smith [7], is necessary for drawing the mucosal graft through the scar tissue under the liver to bring it in contact with the epithelium of the bile ducts. It also provides access to the biliary tree for daily irrigations to prevent sludge formation. The stent tube can be easily removed without reoperation when desired.

Cholecystectomy should be regarded as a major abdominal operation. It should be performed by experienced, humble, trained surgeons and skilled assistants. Familiarity with the abnormalities that can exist in Calot's triangle, with attention to detail during dissection in this area, along with skill in performing an intraoperative cholangiogram, its correct interpretation, and precision in the management of bleeding during cholecystectomy are essential for the prevention of accidental bile duct injuries. For delayed repair of these injuries, hepaticojejunostomy with only 6 weeks stenting gave acceptable results. A 20-month mean follow-up period is relatively short, but the preliminary results of this procedure are quite encouraging.

References

1. Mofti AB, Al-Tameem MM, Al-Khudairy NN, et al. Experience with elective cholecystectomy in King Khalid University Hospital. *Ann Saudi Med* 1987;7:107-10.
2. White TT, Harrison RC. *Reoperative gastrointestinal surgery*. Boston: Little, Brown, 1973;123.
3. Smith EB. Iatrogenic injuries to extrahepatic ducts and associated vessels: a 25-year analysis. *J Natl Med Assoc* 1982;74:735-8.
4. Hermann RE. A plea for a safer technique of cholecystectomy. *Surgery* 1976;79:609-11.
5. Bismuth H. Post-operative strictures of the bile duct. In: Blumgart LH, ed. *The biliary tract*. Edinburgh: Churchill-Livingstone, 1982;209-18.
6. Wexler MJ, Smith R. Jejunal mucosal graft: a sutureless technic for repair of high bile duct strictures. *Am J Surg* 1975;129:204-11.
7. Smith R. Hepaticojejunostomy with transhepatic intubation: a technique for very high strictures of the hepatic ducts. *Br J Surg* 1964;51:186-94.
8. Collins PG, Gorey TF. Iatrogenic biliary stricture: presentation and management. *Br J Surg* 1984;71:980-2.

9. Murley R. The biliary pseudo-trinity. *Aust NZ J Surg* 1984;54:317-20.
10. Kelly CJ, Blumgart LH. Preoperative cholangiography and post cholecystectomy biliary stricture. *Ann R Coll Surg Engl* 1985;67:93-5.
11. Andren-Sandberg A, Alinder G, Bengmark S. Accidental lesions of the common bile duct at cholecystectomy: pre and peroperative factors of importance. *Ann Surg* 1985;201:328-32.
12. Browder IW, Dowling JB, Koontz KK, et al. Early management of operative injuries of the extrahepatic biliary tract. *Ann Surg* 1987;205:649-58.
13. Way LW, Bernhoft RA, Thomas MJ. Biliary structure. *Surg Clin North Am* 1981;61:963-72.
14. Smith R. Obstruction of the bile ducts. *Br J Surg* 1979;66:69-79.
15. Andren-Sanberg A, Johnson S, Bengmark S. Accidental lesions of the common bile duct at cholecystectomy. II. Results of treatment. *Ann Surg* 1985;201:452-5.
16. Smith R. Strictures of the bile ducts. *Proc R Soc Med* 1969;62:131-7.
17. Hertzner NR, Gray HW, Hoerr SO, et al. The use of T-tube splints in bile duct repair. *Surg Gynecol Obstet* 1973;137:413-8.
18. Way LW, Dunphy JE. Biliary stricture. *Am J Surg* 1972;124:287-95.
19. Pilegrini CA, Thomas MJ, Way LW. Recurrent biliary stricture, pattern of recurrence and outcome of surgical therapy. *Am J Surg* 1984;175-80.

SURGICAL MANAGEMENT OF CHIARI MALFORMATION AND SYRINGOMYELIA: EXPERIENCE IN 14 CASES

Naim-Ur-Rahman, FRCS(Eng), FRCS(Edin); Zain Alabedeen B. Jamjoom, MD

قمنا بتحليل خبرتنا مع أربعة عشر مريضاً يعانون من شوه كيارى ومن تكهف النخاع ممن عولجوا في مستشفى الملك خالد الجامعي بين عام ١٩٨٣ و ١٩٩٠م، وذلك من حيث الحالة وقت المراجعة والتدبير العلاجي والملاحظات الجراحية والنتيجة النهائية. ومن الجدير ذكره أننا استبعدنا من هذه السلسلة من كانوا يعانون من قيلة نخاعية سحائية أو تثبت نهاية الحبل الشوكي أو أورام الحبل الشوكي. وقد تم التركيز على التفاوت الكبير في السيرة المرضية والموجودات السريرية في هذه الحالات. تضمنت الدراسات الشعاعية العصبية: التصوير الشعاعي العادي وتصوير النخاع والتصوير المقطعي بالكمبيوتر وكذا التصوير بالرنين المغناطيسي. كان تخفيف الضغط عن الحفرة الخلفية هو العملية الأساسية، واشتملت الإجراءات الأخرى على تحويلة من جوف التكهف إلى المسافة تحت العنكبوتية أو تحويلة بطبانية صفاقية أو قطع الناتئ السني عن طريق الفم أو فغر نهاية الحبل الشوكي. تحسنت حالة أربعة مرضى تحسناً ملموساً عقب الجراحة، ولم تتغير حالة سبعة منهم بينما ساءت حالة ثلاثة مرضى بالرغم من الجراحة.

Our experience with 14 patients afflicted with symptomatic Chiari malformation and syringomyelia, who were treated at King Khalid University Hospital between 1983 and 1990, is analyzed with reference to presentation, management, operative findings, and outcome. Patients with associated myelomeningocele, tethered cord, and spinal cord tumors were excluded from this series. The wide variations in natural history and clinical findings are emphasized. Neuroradiological studies included plain roentgenograms, myelograms, metrizamide-enhanced computed tomograms, and more recently magnetic resonance imaging scans. Posterior fossa decompression was the standard operation; other surgical procedures included syringosubarachnoid shunt, ventriculoperitoneal shunt, transoral odontoid resection, and terminal ventriculostomy. Four patients experienced definite improvement following surgery; the condition in seven was unchanged, and three suffered worsening of the disorder despite operation.

In 1891, Chiari [1] described a patient with herniation of the cerebellar tonsils below the plane of the foramen magnum. His subsequent descriptions defined the spectrum which is currently recognized as type I, II, and III malformations [2]. Arnold [3] later published a similar description of a child with a type II malformation and myelodysplasia. Chiari malformation is one of the more unusual conditions faced by the neurosur-

geon and is characterized by displacement of the cerebellar tonsils and brainstem, to varying degrees, through the foramen magnum. Chiari type II commonly presents in infancy and is associated with spinal dysraphism as well as brainstem cerebral anomalies, while Chiari type I is encountered more commonly in adults. Additional features of this disease include syringomyelia and craniovertebral anomalies. The clinical presentation may be due to Chiari malformation alone or more often to a combination of tonsillar herniation and associated syringomyelia.

Although cystic cavitation of the spinal cord was described over 400 years ago and subsequently named *syringomyelia*, it still remains an obscure condition. There is no complete agree-

From the Department of Surgery, King Khalid University Hospital, King Saud University, Riyadh.

Address reprint requests and correspondence to Dr. Ur-Rahman: Department of Surgery, King Khalid University Hospital, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Accepted for publication 22 August 1990.

ment about the pathogenesis, classification, or even the definition, and this forms a poor basis from which surgical treatment can proceed. Nevertheless, syringomyelia consists of a glial lined cavity within the spinal cord and is of two main types. The first, and by far the most common type, is associated with Chiari malformation and a hydromyelic canal. In the second type, there is no congenital abnormality and cystic cavitation occurs as a result of trauma or arachnoiditis. Most of our patients belonged to the first group.

The majority of Chiari malformation patients harbor a syrinx. Levy et al [4] reported on 127 surgical cases and found that 52 patients had a syrinx. Newman et al [5] reported that 78% of their patients with Chiari malformation had syringomyelia. More recent reports show that 80 to 90% of patients presenting with chronic malformation have an associated syrinx, shown on MR scanning [6].

In recent years, surgery has offered some therapeutic possibilities, with the pathophysiological basis of surgical intervention as follows. The origin of the syringomyelic cavitation lies in the obstruction of the foramina of exit of the fourth ventricle, created by the Chiari malformation, basilar invagination, or arachnoiditis. The distending effect of the ventricular pulse wave on the central canal leads to hydromyelia and rupture of the dilated central canal into the substance of the cord, and this allows cerebrospinal fluid (CSF) to travel along the syringomyelic cavities. Surgical treatment of syringomyelia consists of decompressing the impacted tonsils and opening the foramen of Magendie to permit escape of the confined ventricular fluid, which was previously funnelled into the syrinx. This restores normal flow of CSF.

Clinical Material and Methods

Fourteen patients were operated on by the authors during the last seven years and provide the basis for this review. The patients ranged in age from 11 to 50 years. Males and females were affected equally. The average duration of complaints was 3 years, ranging from 3 months to 10 years. Figures 1 and 2 summarize the symptoms and neurological findings in our patients. Headache and ataxic gait were presenting symptoms in eight patients. Sensory changes and

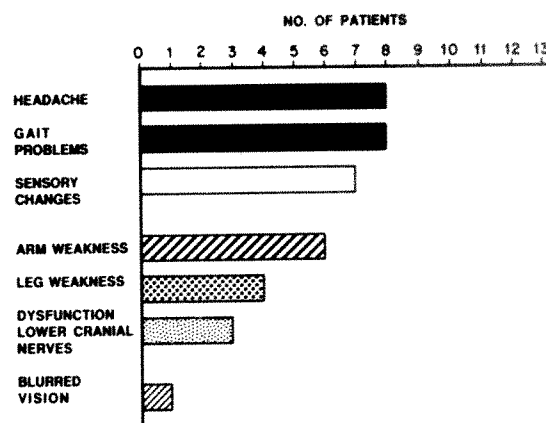


FIGURE 1. Symptoms in 14 patients.

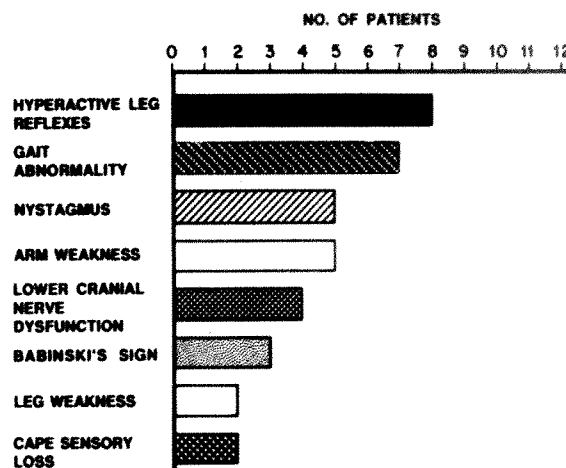


FIGURE 2. Summary of neurological findings in 14 patients.

limb weakness were next in frequency. Lower cranial nerve dysfunction was present in three patients. One patient had blurred vision and papilledema. The most common neurological findings were hyperactive reflexes in the legs and gait abnormality. Nystagmus and arm weakness were next in frequency. Other findings included lower cranial nerve dysfunction, leg weakness, and cape sensory loss (see Figure 2).

Neuroradiological investigations included plain x-ray studies, myelography, non-ionic iodine contrast-enhanced computed tomographic (CT) scans, and more recently, MRI. Plain x-ray films showed basilar impression in four patients, atlanto-occipital fusion in one, vertebral fusion in three, and a widened cervical canal in two.

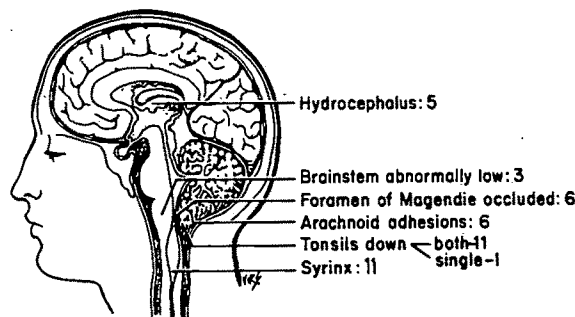


FIGURE 3. Findings at surgery.

Myelographic, CT, and MRI findings correlated closely with operative observations. Figure 3 shows the findings at surgery: tonsillar herniation was present in 12 cases. A definite syrinx was present in 11 cases. Syringomyelia without clear tonsillar herniation was seen only in two cases.

A total of 21 surgical procedures were carried out in 14 patients. Posterior fossa decompression (PFD) was carried out in nine and was combined with cystosubarachnoid shunt in three patients. In two patients, syrinx was the only finding and a shunt was used to drain it. Five patients had a ventriculoperitoneal shunt installed, and one had a transoral resection of odontoid followed by a posterior cervical fusion. One with a very extensive syrinx had terminal ventriculostomy. Although some CSF was seen coming from the cut filum terminale, the patient's condition remained unchanged postoperatively.

Results

Our initial impression of the results of surgery was gratifying, as there was short-term improvement in 50% of the cases. However, longer follow-up and more critical assessment showed that long-term results were less encouraging. As a basis from which to judge the results of treatment, we must examine the natural history of the disease. When viewed against the background of "relentlessly progressive disease" as described by Lord Brain [7], the results of surgery are encouraging, but a more critical review of the natural history in 55 non-surgically treated patients followed for 20 years at the University of Helsinki [8] revealed relatively slow progression with periods of arrest of disease for up to 10 years. Crit-

TABLE 1. Review of surgical series.

Year	Author	No. of patients	Improved	Unchanged	Worsened
1958	Gardner & Angel [9]	74	70%	15%	8%
1970	Hankinson [10]	45	82%	0%	18%
1976	Rhoton [11]	15	0%	94%	6%
1981	Logue & Edwards [12]	61	30%	44%	26%
1983	Levy et al [4]	85	46%	26%	28%
1991	Present series	14	28.5%	50%	22.4%

ical assessment against this background showed that we had four patients with definite and dramatic improvement that could be attributed only to operation. The condition in seven patients stabilized after surgery and in three worsened. Review of other surgical series (Table 1) revealed a remarkable disparity among results. For example, 70% of Gardner and Angel's [9] cases improved after surgery and Hankinson [10] reported improvement in 82% of his operated cases. None of Rhoton's [11] patients improved after surgery.

Illustrative Cases

We describe four representative cases because of their instructive value and to illustrate standard management.

Patient 1

A 20-year-old woman presented with a 5-year history of occipital headache aggravated by coughing and progressive tetraparesis for 5 months, the right side being weaker than the left. She also complained of paresthesias in all four limbs when she bent her head. On examination she had cape sensory loss and there was weakness and wasting of the muscles of both arms. Both legs were weak with bilateral ankle clonus, exaggerated leg reflexes, and extensor plantar responses. While she was still in the hospital, dysphagia developed and she was unable to walk. X-ray studies and tomograms of the skull base showed basilar impression with a high and bulky odontoid process. Myelograms showed an expanded cervical cord and herniated cerebellar tonsils on supine films. CT-metrizamide myelography clearly

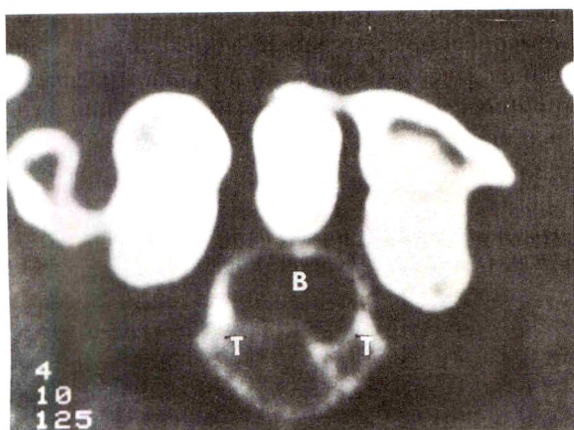


FIGURE 4. Patient 1. Computed tomographic-metrizamide myelography showing asymmetrical herniation of the cerebellar tonsils (TT) well below the level of the foramen magnum and compressing the brainstem (B).

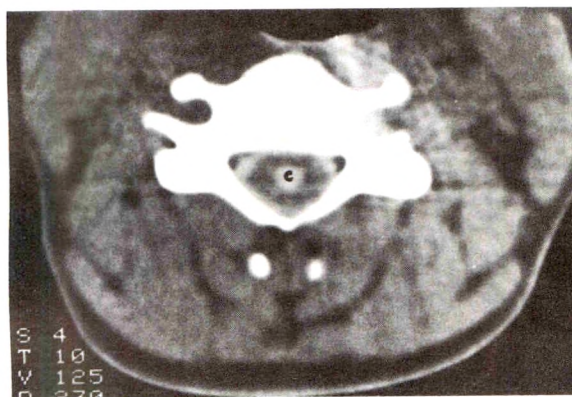


FIGURE 5. Patient 1. Delayed metrizamide-enhanced computed tomographic scan showing contrast filling of the syrinx (c).

demonstrated the tonsillar herniation (Figure 4) as well as contrast filling of the syrinx on delayed films (Figure 5). PFD and upper cervical laminectomy revealed herniated and compressed cerebellar tonsils and loops of posterior inferior cerebellar artery. Postoperatively her deficits reversed steadily. After one month, she was able to eat and walk. A recent outpatient check-up six years after surgery showed her to be asymptomatic, and she has given birth to two children since operation.

Patient 2

This 30-year-old man presented with a three-year history of progressive bilateral arm and leg weakness, nystagmus, ataxic gait, lower cranial nerve paresis, and paresthesias around the shoulders. On examination, he had spastic quad-

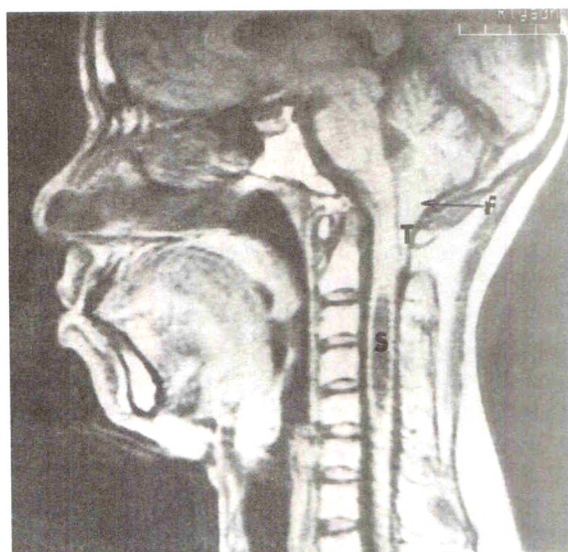


FIGURE 6. Patient 2. Cervical magnetic resonance imaging scan showing syrinx (S) as well as herniation of the cerebellar tonsils (T) below the level of the foramen magnum (F).

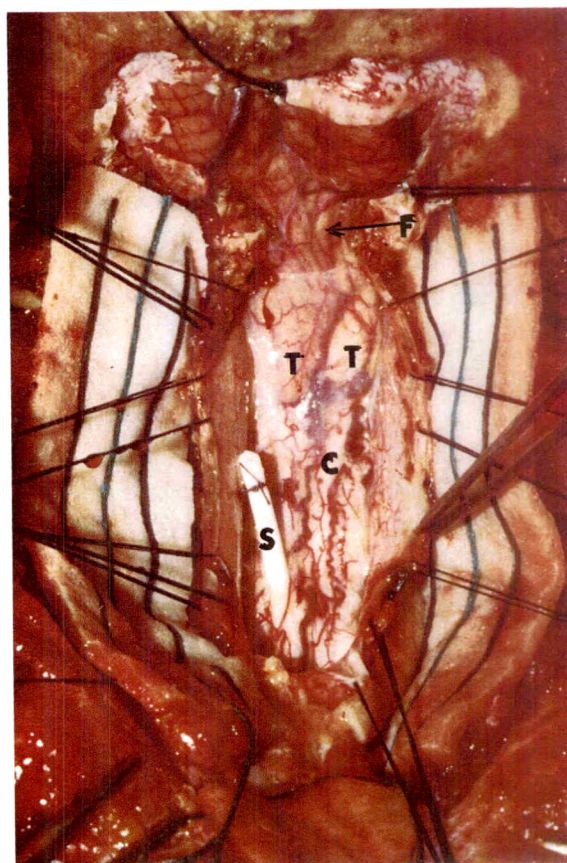


FIGURE 7. Patient 2. Operative findings, showing constriction ring at the foramen magnum (F), herniated cerebellar tonsils (T), and syringosubarachnoid shunt in place (S).

riparexis with some respiratory difficulty. MRI scan (Figure 6) showed syrinx as well as herniated tonsils. PFD and upper cervical laminectomy were carried out. At operation the cerebellar tonsils were found to be markedly compressed at the level of the foramen magnum and were herniated well below this level, the left tonsil being lower than the right (Figure 7). The upper cervical cord was cystic and expanded. A cystosubarachnoid shunt was performed, in addition to PFD. Shunt tubing was introduced into the syrinx and anchored to the inside of the spinal dura mater (Figure 7). Postoperatively the patient's neurological status remained unchanged.

Patient 3

A 35-year-old woman was admitted with a five-year history of progressive weakness of both arms and legs and numbness over the shoulders and all four limbs. Shortly before admission she was unable to walk and became incontinent of urine. On examination she had spastic tetraparesis and patchy sensory loss below the clavicles. Metrizamide-enhanced myelograms and CT scans showed an expanded cervical cord without tonsillar herniation (Figure 8). Cervical laminectomy and installation of a cystosubarachnoid shunt were done. At operation the cord was expanded, cystic, pale, and nonpulsating (Figure 9A). The syrinx was drained by incising the thinnest area. A silastic tube was introduced into the syrinx cavity and anchored to the inside of the dura mater (Figure 9B). Before incising the cord, a needle was introduced into the syrinx cavity and a sample of fluid taken for cell count and protein determination. The protein content in the syrinx fluid was found to be the same as in normal CSF. Drainage of the syrinx led to immediate and notable decompression of the cord as well as a remarkable increase in vascularity, pulsation, and color of the cord (Figure 9B). Postoperatively, the patient showed early improvement in her neurological status and she was able to ambulate with help after four weeks. This early improvement was maintained five years later.

Patient 4

A 20-year-old woman presented with a five-year history of headache. One year prior to admission she noticed increasing weakness and wasting

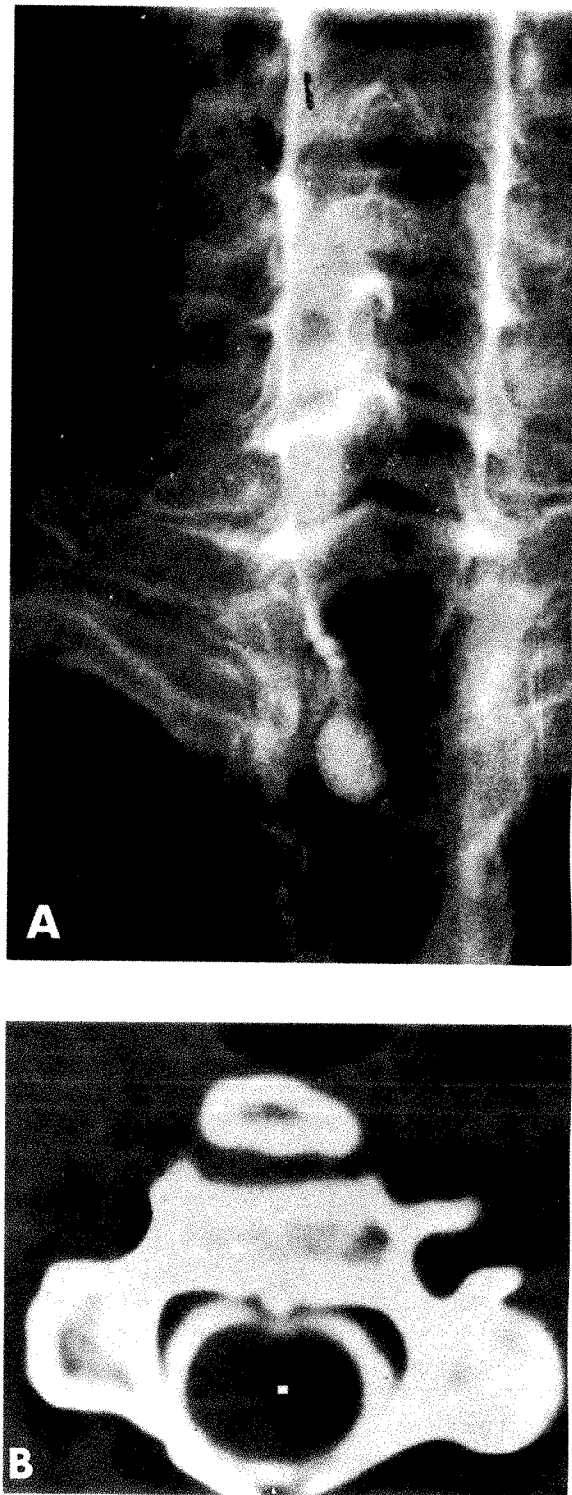


FIGURE 8. Patient 3. (A) Cervical myelogram, showing enormously expanded cord. (B) Post-myelogram computed tomographic scan, showing expanded cervical cord.

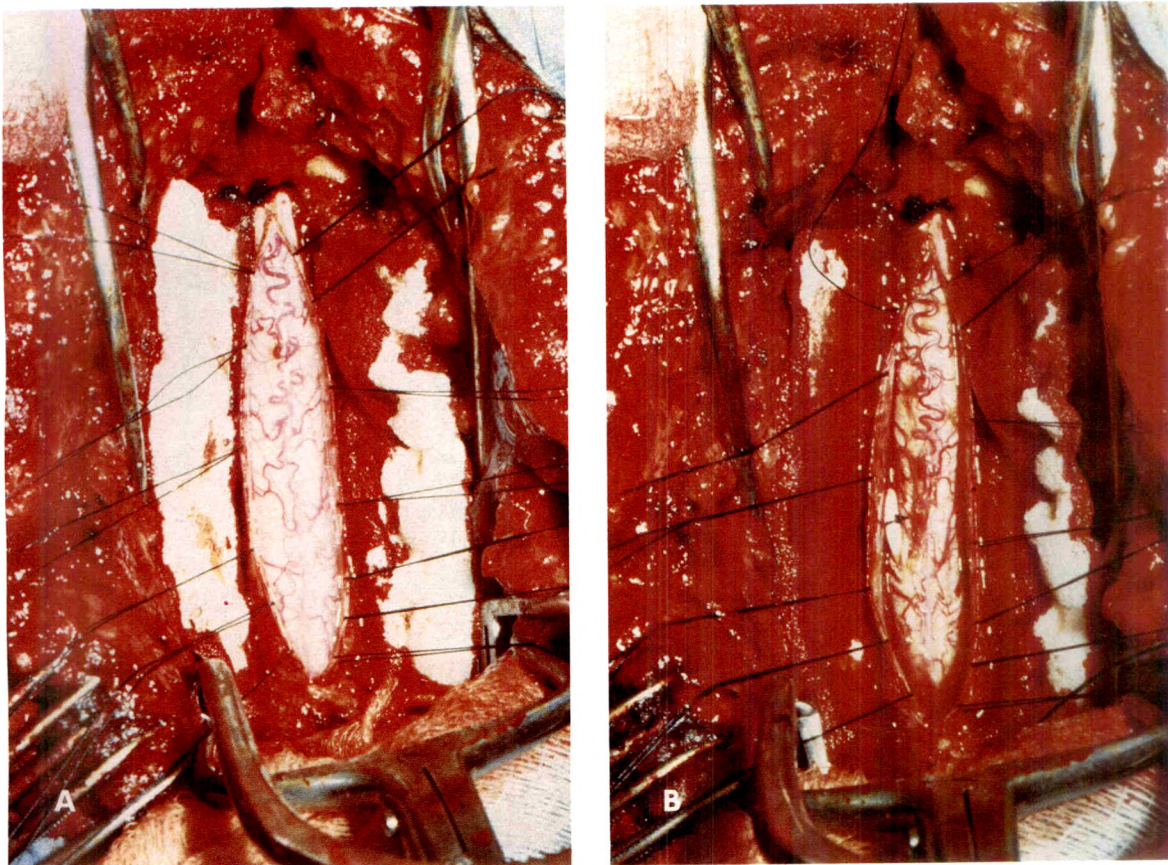


FIGURE 9. Patient 3. (A) Operative view of the posterior aspect of the cervical cord after opening the dura mater, showing expanded pale cystic cord. (B) Cervical cord after drainage of the syrinx by syringosubarachnoid shunt. Note decompression and increased vascularity of the cord and the Silastic tube draining the syrinx.

of both arms (right more than left) as well as difficulty in walking and occasional incontinence of urine. On admission, she had spastic paraparesis and incontinence of urine, and was unable to walk without assistance. Both arms were weak and wasted. Cerebellar dysfunction was indicated by the presence of nystagmus and limb ataxia. There were no objective sensory abnormalities, although she complained of numbness and paresthesia over the shoulders and legs. A cervical MRI scan showed herniation of the cerebellar tonsils and brainstem well below the level of the foramen magnum as well as extensive cavitation of the whole cervical cord (Figure 10). The fourth ventricle was notably dilated. An MRI scan of the brain showed marked hydrocephalus (Figure 11). We chose to install a ventriculoperitoneal shunt at the initial procedure, but informed the patient that a second operation for posterior fossa decompres-

sion might be needed at a later stage. There was immediate postoperative improvement following the shunting procedure. Both subjective and objective improvement in her neurological status was clearly evident. Two weeks after surgery, her headache resolved and she was fully continent of urine. This clinical improvement was accompanied by reduction in the ventricular and syrinx size on postoperative radiological studies. She is still under observation, and if this improvement persists, the PFD will be unnecessary.

Discussion

Merritt's [13] textbook of neurology classified syringomyelia as a degenerative process for which "there is no satisfactory treatment," and Lord Brain [7] described it as a "relentlessly progressive disorder." It was against this background and in

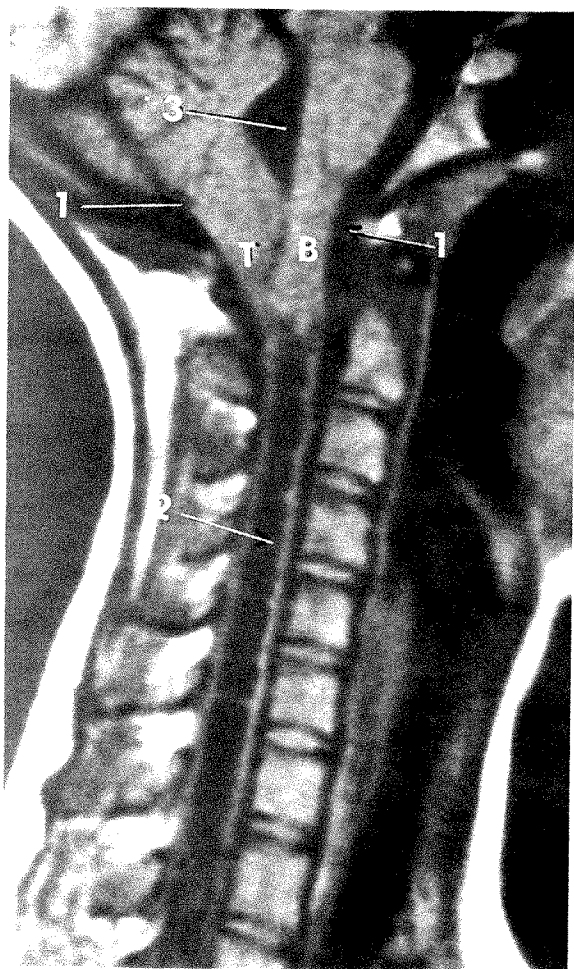


FIGURE 10. Patient 4. Cervical magnetic resonance imaging showing: (1) herniation of the cerebellar tonsils (*T*) and brainstem (*B*) below the level of the foramen magnum; (2) extensive cavitation of the whole cervical cord; and (3) dilated fourth ventricle.

the light of more recent attempts to explain the pathogenesis of syringomyelia and Chiari malformation that many appealing surgical techniques have been developed to offer some hope of cure or arrest of this condition.

Theories that explain the pathogenesis of the Chiari malformation and syringomyelia include both developmental and acquired etiologies. Gardner [14,15] attributed the hindbrain ectopia to failure of the rhombic roof to perforate. This failure results in absent or stenotic foramina of Magendie and Luschka. With this closure of the foramina of exit, the CSF is driven distally by the arterial pulsations transmitted via the choroid. This acts as a hydrodynamic force displacing the

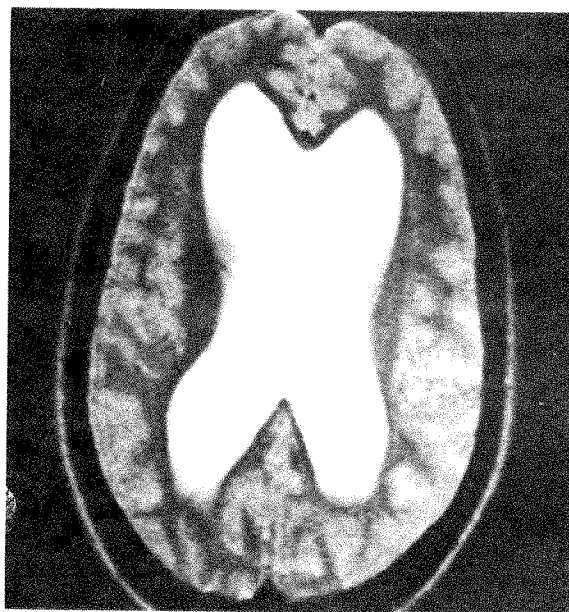


FIGURE 11. Patient 4. Magnetic resonance imaging scan of brain, showing marked hydrocephalus.

hindbrain structures caudally through the foramen magnum and distending the central canal of the spinal cord. Williams [16] suggested that birth trauma leads to subarachnoid hemorrhage and subsequent basilar arachnoiditis, resulting in obstruction of CSF outflow from the fourth ventricle to the cisterns. This restriction of the CSF flow at the foramen magnum causes dissociation of craniospinal pressure. Differential pressures between the cranial and spinal compartments during straining and coughing act to displace the hindbrain caudally and distend the central canal. Thus, Williams implicates acquired abnormalities as the cause of the Chiari malformation and syringomyelia. In our opinion, none of these developmental or acquired factors explain completely the origin and clinical features of this condition.

We will attempt here to correlate the clinical features, diagnostic evaluation, and surgical treatment with the abnormal anatomy and pathophysiology of this condition. The information presented is a compilation of several published series and our own data.

Headache and neck pain are present in the majority of cases of Chiari malformation (present in 57% of our cases). Headache may be a constant occipital one, reflecting irritation of the dura mater of the posterior fossa or a paroxysmal pain

due to alterations in CSF pressure. Hydrocephalus, present in 10% of patients with Chiari malformation [6], and found in 35% of our cases, produces more constant, chronic bifrontal headache. Cough headache with cough syncope due to sudden CSF pressure variation and infarction of the foramen magnum tissue were seen in only one of our patients. Symptoms and signs referable to the lower brainstem and cerebellar dysfunction were present in about half of our patients. These findings are due to direct brainstem compression at the foramen magnum, to brainstem ischemia, or less commonly, to syringobulbia. Brainstem features include nystagmus, vertigo, diplopia, hoarseness, dysphasia, and tongue atrophy, and these reflect involvement of the nuclei of cranial nerves VI, VII, IX, X, XI, and XII and their neural connections.

Scoliosis is commonly associated with syringomyelia [17] but was present in only one of our cases. Chronic paraspinal muscle imbalance due to cord injury produced by the syrinx is the basis for this spinal deformity. Charcot joints form as the result of anesthetic joint destruction [18]. Sensorimotor disorders are found in the majority of patients and were encountered in nearly all our patients. They result from the involvement of corticospinal tracts, anterior horn cells, posterior columns, and spinothalamic tracts. Deficits may be due to direct compression at the cervicomedullary junction by the impacted tonsils, to brainstem and spinal cord ischemia, or to gliosis due to compression of the anterior spinal and posterior inferior cerebellar arteries (both of which traverse the impacted foramen magnum). Deficits may also be caused by spinal cord displacement and destruction by a syrinx cavity. Weakness, present in most of our cases, was associated with spasticity and hyperreflexia in the legs caused by corticospinal tract lesion, or was associated with atrophy and fasciculations in the arms resulting from anterior horn cell destruction. Weakness and atrophy of the upper limbs along with a suspended, cape-like sensory loss and dissociated posterior column and spinothalamic dysfunction constitutes the classic syringomyelic syndrome [7,13]. All or part of this syndrome, along with spastic or ataxic gait, areflexic upper extremities, brisk lower limb reflexes with clonus and extensor plantar responses, was observed in most of our cases.

Diagnostic evaluation techniques have evolved over the years. Cahan and Bentson [17] describe the abnormalities seen on skull and cervical spine x-ray studies, Pantopaque-enhanced and air myelography in supine and sitting positions, and vertebrae angiography. Currently these procedures are rarely used, having been replaced by CT, non-ionic iodine contrast myelography, and MRI. CT-contrast myelography, when performed with immediate and six-hour delayed scanning, commonly detects a syringomyelic cavity as well as tonsillar herniation. MRI has now become the investigation of choice and provides excellent details of the brainstem, spinal cord, tonsillar herniation, and syrinx.

Many types of surgical procedures and techniques are available to treat the Chiari malformation and syringomyelia. This series is unique, as almost all the known methods of surgical management have been used. The surgeon must individualize the therapeutic options in each patient. Surgery is clearly indicated in symptomatic patients with progressive neurological deficits. Our recommendation is that patients with marked hydrocephalus should receive a ventriculoperitoneal shunt as the initial procedure, because marked improvement and collapse of the syrinx may be produced by this procedure, as happened in two of our cases. Most of the patients with Chiari malformation with or without syringomyelia undergo PFD. The technique in use has evolved from operative procedures described by Bertrand [19], Hankinson [10], Gardner and Angel [9], and Williams [16] and consists of a suboccipital craniectomy with an upper cervical laminectomy that is sufficient enough to decompress the cerebellar tonsils completely and open the foramen of Magendie to allow free exit of the CSF from the fourth ventricle. This usually involves a laminectomy of the C1 and occasionally the C2 laminar arch. A dural graft was used by one of the authors (ZJ). A cystosubarachnoid shunt is combined with PFD only when the syrinx is large and presents in the operative field. A cystosubarachnoid shunt alone was used in patients with syringomyelia who didn't have Chiari malformation. Terminal ventriculostomy was used for a very extensive syrinx extending into the filum terminale, and although CSF was seen exiting from the cut filum, the patient's condition remained

unchanged postoperatively. Indications for this procedure are less well defined. Williams and Fahy [20] reported 31 cases of terminal ventriculostomy. They found it difficult to establish the communication of the syrinx with the fourth ventricle, and only three cases had clear-cut improvement.

Review of the literature as well as our own experience shows that the conditions of approximately one quarter of the patients continue to deteriorate despite surgery. It is known that there is more than one distinct etiology, including the hydrodynamic theory which forms the basis of all the surgical procedures. In these patients who do not benefit from operative intervention aimed at correcting these hydrodynamic forces, some other abnormality must be at work. We suggest that the ischemic/degenerative damage due to compression of the anterior spinal artery and posterior inferior cerebellar artery, both of which are compressed at the tightly obstructed foramen magnum, constitutes the primary lesion in these cases, compression of the posterior inferior cerebellar artery being responsible for the lower brainstem and cerebellar signs and compression of the anterior spinal artery leading to the ischemic/degenerative lesion of the cord with secondary gliosis and cavitation. The common association of bulbar symptoms with syringomyelia has often led to the diagnosis of syringobulbia. From the standpoint of MRI correlation and our own experience, we conclude that bulbar dysfunction is not caused by rostral bulbar extension of the syrinx but is due to lower brainstem ischemia caused by vascular compression. The implication of this suggestion is that we are dealing with two populations of patients with two distinct etiologies: those with active hydrodynamic forces who can be helped by operation and those who have sustained ischemic/degenerative damage that cannot be reversed. The challenge is to test this thesis and identify the criteria for distinguishing those patients who would benefit from surgery.

References

1. Chiari H. Ueber Vernderungen des Kleinhirns infolge von Hydrocephalie des Grosshirns. *Dtsch Med Wochenschr* 1891;17:1172-5.
2. Chiari H. Ueber Vernderungen des Kleinhirns, des Pons und der Medulla Oblongata infolg von congenitaler Hydrocephalie des Grosshirns. *Denschr Akad Wiss Wien* 1896;63:71-116.
3. Arnold J. Myelocyste. Transposition von Gewbskeimen von Gewbskeimen und Sympodie. *Beitr Pathol Anat Allg Pathol* 1894;16:1-21.
4. Levy WJ, Mason L, Hahn JF. Chiari malformation presenting in adults: a surgical experience in 127 cases. *Neurosurgery* 1983;12:377.
5. Newman PK, Terenty TR, Foster JB. Some observations on the pathogenesis of syringomyelia. *J Neurol Neurosurg Psychiat* 1981;44:964.
6. Halamandaris GG, Batzdorf U. Adult Chiari malformation. *Contemp Neurosurg* 1989;11(26):1-6.
7. Brain WR. *Brains' disease of the nervous system*, ed 7. London: Oxford University Press, 1970.
8. Boman K, Livanainen M. Prognosis of syringomyelia. *Acta Neurol Scand* 1967;43:61-8.
9. Gardner WJ, Angel J. The cause of syringomyelia and its surgical treatment. *Cleve Clin Q* 1958;25:4-17.
10. Hankinson J. Syringomyelia and the surgeon. In: Williams D, ed. *Modern Trends in Neurology*. London: Butterworth, 1970;5:127-48.
11. Rhon A Jr. Microsurgery of Arnold Chiari malformation in adults with and without hydromyelia. *J Neurosurg* 1976;45:473-83.
12. Louge V, Edwards ME. Syringomyelia and its surgical treatment. *J Neurol Neurosurg Psychiatry* 1981;44:273-84.
13. Merritt HH. *A textbook of neurology*, ed 5. Philadelphia: Lea & Febiger, 1973;513.
14. Gardner WJ, Angel J. The mechanism of syringomyelia and its surgical correction. *Clin Neurosurg* 1958;6:131.
15. Gardner WJ. Hydrodynamic mechanism of syringomyelia. *J Neurol Neurosurg Psychiatry* 1965;28:247.
16. Williams B. Progress in syringomyelia. *Neurol Res* 1986;8:130.
17. Cahan LD, Bentson JR. Considerations in the diagnosis and treatment of syringomyelia and Chiari malformation. *J Neurosurg* 1982;57:24.
18. Kolawole T, Banna M, Hawas N, Naim-ur-Rahman. Neuropathic arthropathy as a complication of syringomyelia. *Br J Radiol* 1987;60:702-4.
19. Bertrand G. Dynamic factors in the evolution of syringomyelia and syringobulbia. *Clin Neurosurg* 1973;20:322.
20. Williams B, Fahy G. A critical appraisal of "terminal ventriculostomy" for the treatment of syringomyelia. *J Neurosurg* 1983;58:188-97.

THE VALUE OF OLIGOCLONAL BANDS IN NEUROBRUCELLOSIS

Abdul Kader Daif, MD

قمنا بإجراء رحلان هلامي كهرساوي على مصول مخففة وعينات غير مركزة من السائل المخي النخاعي أخذت من عشرة مرضى مصابين بداء البروسيالات العصبي، وعشرة مرضى مصابين بتصلب متعدد، وسبعة يعانون من الإصابة العصبية بمتلازمة بهجة وخمسة مصابين بالتهاب السحايا السلي وثلاثة يعانون من اضطرابات عصبية أخرى. وقد ساندت بياناتنا النظرية القائلة بتكون الغلوبولينات المناعية داخل القرباب في حالة الإصابة بداء البروسيالات العصبي، كما أظهرت الدليل على أن وجود أشرطة الغلوبولين المناعي IgG قليلة النسائل في السائل المخي النخاعي والمصل تشكل تأكيدا سريعا ومفيدا على تشخيص الإصابة بداء البروسيالات العصبي.

We performed polyacrylamide gel isoelectric focusing on diluted sera and non-concentrated CSF from ten patients with neurobrucellosis, ten patients with definite multiple sclerosis, seven patients with neuro-Behcet's syndrome, five patients with tuberculous meningitis, and eight patients with other neurological disorders. Our data support the proposed theory of the intrathecal synthesis of immunoglobulins in the presence of neurobrucellosis, and showed that evidence of oligoclonal IgG bands in cerebrospinal fluid and serum provides rapid and helpful confirmation of diagnosis of neurobrucellosis.

The differential diagnosis of infections of the central nervous system (CNS) with *Mycobacterium tuberculosis* and *Brucella* continues to pose serious practical problems in places where *Brucella* and tuberculosis are endemic. In addition, multiple sclerosis, a disease for which there is as yet no single diagnostic test, may be difficult to distinguish from neuro-Behcet's syndrome manifesting in the CNS alone, because of the similar clinical manifestations and paraclinical findings of the two disorders. In view of this, an objective test which assists in distinguishing these conditions is highly desirable. The presence of oligoclonal IgG, as demonstrated by agarose gel electrophoresis or polyacrylamide gel isoelectric focusing, is a well-recognized phenomenon exhibited by various inflammatory diseases of the CNS, and most probably reflecting antibody synthesis within the cere-

brospinal fluid (CSF) pathways [1,2]. The purpose of this study was to ascertain the presence of oligoclonal IgG bands (IgG/OB) in the CSF and sera of patients with neurobrucellosis.

Patients and Methods

A total of 39 patients were included in this study, and the clinical details are as follows:

Group 1 consisted of ten patients with CNS brucellosis. Each patient had a history of ingesting raw milk from cows, sheep, goats, or camels, and fulfilled the diagnostic criteria for neurobrucellosis. These criteria were: (1) symptoms and signs of neurological disease; (2) raised serum and CSF brucella titer of greater than 160; (3) either positive or negative blood and CSF culture; (4) remission or improvement with anti-*Brucella* treatment. The presenting clinical manifestations of these patients and their paraclinical investigations are described in Table 1.

Group 2 were made up of four patients who had definite tuberculous meningitis. Ten patients with definite multiple sclerosis comprised Group 3, and the disease was diagnosed according to Poser

From the Department of Neurology, College of Medicine, King Saud University, Riyadh.

Address reprint requests and correspondence to: Dr. Daif, Department of Neurology (38), King Khalid University Hospital, P.O. Box 7805, Riyadh 11472, Saudi Arabia.

Accepted for publication 22 August 1990.

TABLE 1. *Characteristics of patients with neurobrucellosis.*

Patient no.	Age (yr)/sex	Clinical presentation	CSF cell count ($\times 10^9/L$)	CSF protein (g/L)	CSF glucose (mmol/L)	IgG index 0.7	Brucella titer
1	26/M	Meningopolyradiculo-neuropathy	520	1.4	1.80	0.8	S:1/160; CSF 1/320
2	40/M	Acute confusional state	140	5.1	0.97	1.2	
3	19/M	Polyradiculoneuropathy, truncal ataxia, and neurogenic deafness	180	5.9	0.89	1.3	S:1/320; CSF 1/320
4	20/M	Bilateral papilledema	225	4.1	6.49	1.1	S:1/2560; CSF 1/640
5	31/M	Bilateral papilledema	290	1.75	3.10	0.8	S:1/1280; CSF 1/640
6	28/F	Acute urinary retention	300	1.6	2.50	0.8	S:1/2650; CSF 1/650
7	24/M	Lateral lumbar disc prolapse	124	0.90	1.25	0.8	S:1/320; CSF 1/320
8	40/M	Canda equina syndrome	100	0.8	3.25	0.8	S:1/320; CSF 1/320
9	30/M	TIA's in the anterior circulation and alternate hemiparesis	220	2.5	2.50	1.0	S:1/640; CSF 1/320 and CSF culture +
10	25/F	Cerebrovascular accident, right MCA	120	1.7	1.40	0.9	S:1/320; CSF 1/320

M = male; F = female; S = serum; CSF = cerebrospinal fluid; MCA = middle cerebral artery; TIA = transient ischemic attack.

et al's [3] criteria. Group 4 consisted of seven patients with neuro-Bechet's syndrome, diagnosed according to O'Duffy's [4] criteria. Group 5 represented eight patients with other neurological disorders: two with chronic headache, two with vertigo, two with chronic myelography of unknown cause, and two patients with vertigo and peripheral polymyopathy.

Results

All but one of the specimens of CSF and serum from patients with neurobrucellosis showed IgG/OB in either the CSF and sera. In two patients, IgG/OB was still detected in both the CSF and serum after one month in one patient and six months in the other after successful anti-*Brucella* therapy.

In the group of patients with multiple sclerosis, IgG/OB was detected in only the CSF of all ten patients. However, IgG/OB was not detected in CSF or serum in any patients from Groups 2, 4, or 5 (tuberculosis, neuro-Bechet's, other neurological diseases) (Table 2).

TABLE 2. *Comparison of laboratory data.*

Variations ^a	NB (N = 10)	MS (N = 10)	N-B (N = 7)	TBM (N = 4)
CSF IgG/OB	9	10	0	0
Serum IgG/OB	9	0	0	0
IgG index > 0.7	10	10	2	1
CSF cells > $5 \times 10^9/L$	10	9	4	4
CSF protein < 0.45 gm/L	0	1	0	1
CSF glucose < 50 mmol/L	7	0	0	3

^aValues in parentheses represent reference values.

NB = neurobrucellosis; MS = multiple sclerosis; TBM = tuberculous meningitis; N-B = neuro-Bechet's syndrome; CSF = cerebral spinal fluid; IgG/OB = oligoclonal immunoglobulin G bands.

Discussion

The humoral immune response in the CNS occurs regardless of the source of infection. It has been observed in parasitic, bacterial, viral, and fungal infections and in noninfective disorders such as multiple sclerosis [5,6]. However, the CSF electrophoretic patterns in these diseases are

quite different due to variable degrees of breakdown of the blood-CSF barrier as a consequence of the inflammatory process. The IgG index may be helpful in demonstrating local production of immunoglobulins in CSF in spite of an increased CSF total protein level [7,8]. The significance of IgG/OB has been studied extensively in the context of multiple sclerosis and subacute sclerosing panencephalitis, and there is no doubt about its close relationship to the intrathecal synthesis of immunoglobulins in these conditions [4,9]. The follow-up electrophoretic findings in our Patients 6 and 10 emphasize the nature of the underlying immunological process in the light of the persistent IgG/OB and increased IgG after remission of the inflammation. This is marked by the disappearance of transudative features from the electrophoretic pattern. The persistence of CSF IgG/OB in patients with diagnosed brucellosis should indicate a high risk of chronic-progressive neurological symptoms secondary to persistent specific antigenic or autoantigenic local stimulation. This raises the practical question as to whether to treat such patients again or to use additional medication.

The diagnosis of neurobrucellosis presents a challenge to the clinician, as the clinical features and CSF findings may be confused with CNS infections with mycobacteria, treponema, or fungi [10-12]. Culture of *Brucella* from CSF provides a definitive diagnosis, but this procedure usually takes 4 to 6 weeks and has a low yield (1/10 of our patients), possibly because of previous exposure to antibiotics.

This study shows that the demonstration of IgG/OB in CSF and serum is a rapid test which can be used as an important index in the diagnosis of neurobrucellosis at the time of presentation.

Acknowledgments

I would like to express my appreciation and thanks to Dr. Peter Hodgson and Prof. Mohsen Hazmi for their advice and review of the manuscript; also, to Lydia Gallardo for secretarial assistance.

References

1. Link H. Immunoglobulin G and low molecular weight proteins in human cerebrospinal fluid: chemical and immunological characterisation with special reference to multiple sclerosis. *Acta Neurol Scand* 1967;28(suppl):1-136.
2. Link H. Some aspect of immune reactions of brain. Rose CF, ed. *Clinical Neuroimmunology*. Oxford: Blackwell, 1979;12-28.
3. Poser CM, Paty DW, Scheinberg L. New diagnostic criteria for multiple sclerosis: guidelines for research protocol. *Ann Neurol* 1983;13:227-31.
4. O'Duffy JD, Goldstein NP. Neurologic involvement in seven patients with Behcet's disease. *Am J Med* 1976;61:170-4.
5. Tourtellotte WC. On cerebrospinal fluid immunoglobulin G (IgG) quotients in multiple sclerosis and other diseases: a review and a new formula to estimate the amounts of IgG synthesized per day by the central nervous system. *J Neurol Sci* 1970;10:279-304.
6. Link H, Muller R. Immunoglobulins in multiple sclerosis and infections of the nervous system. *Arch Neurol* 1971;25:325-44.
7. Delpech B, Lichtblau E. Etude quantitative des immunoglobulins G et de l'albumine du liquid cephalo-rachidien. *Clin Chim Acta* 1972;37:15-23.
8. Christensen O, Clausen J, Fog T. Relationships between abnormal IgG index, oligoclonal bands, acute phase reactants and some clinical data in multiple sclerosis. *J Neurol* 1978;218:237-44.
9. Culter RWP, Merler E, Hammerstad JP. Production of antibody by the central nervous system in subacute sclerosing panencephalitis. *Neurology* 1968;18(2):129-32.
10. Al-Deeb S, Yaqub B, Sharif H, Al-Rajeh S. Neurobrucellosis. In: Vinker PJ, Bruyn GW, Klawans HL, eds. *Handbook of Clinical Neurology*, vol. 8. Amsterdam: North Holland, 1988;581-603.
11. Young EJW. Human brucellosis. *Rev Infect Dis* 1983;5:821-42.
12. Silva CA, Rio ME, Goncalves DM. Oligoclonal gamma globulin of cerebrospinal fluid in neurobrucellosis. *Acta Neurol Scand* 1980;61:42-8.

COMPARATIVE RESPONSES OF PLASMA GLUCOSE, INSULIN AND C-PEPTIDE FOLLOWING INGESTION OF ISOCALORIC GLUCOSE, A MODIFIED URBAN SAUDI BREAKFAST AND DATES IN NORMAL SAUDI PERSONS

Mohammed Ahmed, MD, FACP; Abdulaziz Al-Othaimeen, MPH;
Edward De Vol, PhD; Alan Bold, MD

ينصح مرضى السكر عادة بتجنب تناول التمور دون سند علمي. فكرنا في أهمية التعرف على العواقب الاستقلابية لتناول التمر لدى الأصحاء من السعوديين قبل الشروع بإجراء دراسات على المصابين بالسكري. قمنا باختبار تسعة عشر شخصاً صحيحاً، ١١ من الذكور و ٨ من الإناث، أعمارهم 29.4 ± 1.5 (متوسط $\pm$ الخطأ المعياري للمتوسط) ومنسب كتلة الجسم 22.1 ± 0.5 ، وذلك بإطعامهم إحدى الوجبات التالية بتوزيع عشوائي: (أ) وجبة تمر مكونة من حوالي ٣٠٠ كالوري (الكربوهيدرات ٧٤.٥ غ، البروتينات ٣.٧ غ والدهون ٠.٦٦ غ)، (ب) وجبة فطور سعودية حضرية معدلة من ٣٠٠ كالوري (الكربوهيدرات ٣٥.٦ غ، البروتينات ١٣.١٦ غ والدهون ١.١٩ غ)، (ج) ٧٥ غرام من محلول الغلوكوز يحتوي على ٣٠٠ كالوري أيضاً (اختبار تحمل الغلوكوز عن طريق الفم) على ثلاثة أيام مختلفة يفصل بين كل منها أسبوع على الأقل. وقد تم تحديد قيم الغلوكوز والإنسولين والبيتيد (ج) قبل ثلاثين دقيقة من الوجبة وعند بدئها ثم كل ٣٠ دقيقة لفترة ١٨٠ دقيقة. كما تم تحديد مناسب سكر الدم بالنسبة لوجبة التمر ووجبة الفطور المعدلة. لم تكن الرسوم البيانية للغلوكوز والإنسولين والبيتيد (ج) مختلفة بين وجبة التمر والوجبة المعدلة ولكنها كانت مختلفة مقارنة باختبار تحمل الغلوكوز عن طريق الفم. وتجدر الإشارة إلى أن هذه هي المرة الأولى التي يتم فيها توثيق مناسب سكر الدم بالنسبة للتمر. وفيما يتعلق بالتمر من نوع «خلاص» فقد كان المنسب 57.7 ± 8.5 وكان أقل بكثير منه في وجبة الفطور المعدلة الذي كان 79.0 ± 8.5 . خلافاً للاعتقاد السائد، تدحض هذه الدراسة الفكرة القائلة بأن تناول التمر يؤثر سلباً على تحمل الغلوكوز لدى الأصحاء إذا ما قورن بوجبة الفطور المعدلة. وقد شوهدت نتائج مماثلة في الدراسات الأولية على مرضى السكر في مختبرنا.

Diabetic patients are commonly advised without scientific basis to avoid ingestion of dates. Prior to undertaking studies in diabetic persons, we considered it important to establish the metabolic consequences of date ingestion in normal Saudi subjects. Nineteen normal subjects, 11 males and 8 females, aged 29.4 ± 1.5 (mean $\pm$ SEM) with a body mass index (BMI) of 22.1 ± 0.5 were fed in a random order: a) a date meal (DM) consisting of approximately 300 calories (Carbohydrates - CHO 74.5 g, proteins 3.7 g and fats 0.66 g), b) a modified urban Saudi breakfast (SBF) 300 calories (CHO 35.6 g, proteins 13.16 g and fats 11.9 g), and c) a 75 g glucose solution - 300 calories (oral glucose tolerance test - OGTT), on 3 different days at least 1 week apart. Plasma glucose (G), insulin (I) and C-peptide (C) values were determined at -30, 0 and then every 30 minutes for 180 minutes. Glycemic indices for DM and SBF were also determined. G, I and C area profiles were not different between DM and SBF but were when compared with OGTT. This is the first documentation of the glycemic index for dates. For the "Khalas" variety it was found to be 57.7 ± 8.5 and was significantly lower than that for SBF which was 79.0. Contrary to the usual belief, this study refutes the notion that ingestion of dates adversely affects glucose tolerance compared with SBF in normal subjects. Similar results are observed in preliminary studies in diabetic subjects in our laboratory.

From the Departments of Medicine (Dr. Ahmed), Food and Nutrition. Department (Mr. Al-Othaimeen), Biomedical Statistics and Scientific Computing (Dr. De Vol), and Pathology and Laboratory Medicine (Dr. Bold), King Faisal Specialist Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Ahmed: Section of Endocrinology & Metabolism, Department of Medicine, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.
Accepted for publication 28 August 1990.

Recently there has been a surge of interest in the effects of both different CHO foods and mixed meals on postprandial plasma glucose and insulin responses and the implications of these factors for the diabetic diet [1,2]. Considering the historical, socioeconomic and nutritional value of dates, the fruit of the tree *Phoenix dactyliferous*, it is surprising that, to our knowledge, there is no available information on the metabolic responses to the ingestion of this fruit either in normal or diabetic subjects. Gathering such information is of urgent importance to examine the glycemic responses of date ingestion both in normal and diabetic persons.

Diabetic patients are commonly advised to avoid ingestion of dates to prevent presumed wide fluctuations in plasma glucose. However, there is no scientific evidence available to validate such a dietary restriction. Prior to undertaking studies in diabetic persons, we considered it important to establish metabolic consequences of date ingestion in normal Saudi subjects. The aims of the study were a) to examine plasma glucose (G), insulin (I) and C-peptide (C) responses following an acute challenge of date meal (DM) ingestion; b) to compare circulating G, I and C responses following DM ingestion versus 1) a meal of almost identical calories but of usual composition consumed in an urban style Saudi breakfast (SBF); 2) an isocaloric glucose solution.

It is hoped that this information will help formulate principles of healthy diet in normal Saudi subjects and also provide physiological information necessary to design principles of diet therapy in Saudi diabetic patients.

Material and Methods

Nineteen normal Saudi subjects, 11 males and 8 females, aged 29.4 ± 1.5 (range 23–48) years with a BMI of 22.1 ± 0.5 (range 17.2–25.0) were fed in a random order, (a) DM consisting of approximately 300 calories of "Khalas" variety dates (CHO 74.5 g, protein 3.7 g and fats 0.66 g), (b) 300 calories of SBF (CHO 35.6 g, protein 13.16 g and fats 11.9 g), and (c) 300 calories (75 g) of glucose solution (OGTT) on three different days, at least one week apart, in a metabolic unit. On the basis of detailed interviews of normal Saudi volunteers (resident physicians and hospital employees), we defined their usual breakfast and designed the

same for the study. This consisted of orange juice, boiled egg, Arabic bread, hot whole milk and Arabic coffee, which we have designated as a modified urban Saudi breakfast. Plasma G, I and C values were determined at -30, zero and then every 30 minutes for 180 minutes in relation to the administration of each diet. Incremental areas above baseline for 180 minutes for G, I and C were determined, as well as the glycemic indices for DM and SBF.

"Khalas" dates cultivated on our hospital premises were harvested as tree-ripe fresh soft fruit. The fruit was harvested six months previously, in September 1988, washed thoroughly and after a lapse of 4 days only the medium ripe dates were stored at -20 degrees centigrade. Following an overnight thawing it was determined that the storage process had resulted in a net weight loss of 15% from dehydration. The subjects were fed 110 g dates the next morning. Dry matter (88.7%) in "Khalas" dates is composed predominantly (76%) of CHO [3]. The content of reducing sugars in this variety of dates is reported to be 51–59% [3,4]. Simple sugars (mono and disaccharides) contained in "Khalas" dates consist of glucose 32.4%, fructose 27% and sucrose 16.8% and the net glucose/fructose ratio is 1.2 [4]. The approximate composition of 110 g "Khalas" dates according to the published data [3,4] is as follows: dry weight 98 g, total CHO 74.5 g, glucose 31.8 g, fructose 26.5 g, sucrose 16.5 g, polysaccharide hydrolysate 7 g, proteins 3.7 g, fats 0.66 g and fiber 2.4 g.

Incremental areas above baseline for G, I and C as well as the glycemic indices for the DM and SBF were determined. The incremental area under the curve was taken to be the area above the fasting value calculated geometrically. Any area beneath the fasting value was ignored.

The GI has been defined as the area under the plasma glucose response curve for a test food divided by the area under the plasma glucose curve for an equivalent amount of CHO derived from a standard reference food taken by the same individual $\times 100$ [5]. The amount of available CHO in the DM and the reference food (glucose solution) was almost identical (75 g) but in the SBF it was 35.6 g. GI for SBF was calculated as described by previous investigators [1,6]. The contribution of each food item to the CHO content of the SBF was calculated (19.7% of the total

CHO was derived from orange juice, 5.4% from milk, 0.6% from egg, and 9.9% from Arabic bread). The proportion of CHO contributed by each item was multiplied by its GI, obtained from published data [1,7] to give the item's contribution to the meal GI. The GI values of the individual food items were summated to give the total meal GI ($19.7/35.6 \times 80$ for orange juice, $5.4/35.6 \times 49$ for milk and $9.9/35.6 \times 99$ for bread = total GI of 79 for the SBF).

Assays

Plasma G was determined in duplicate on a Hitachi 737 Analyzer by a standard hexokinase method. Plasma I & C were measured in duplicate by standard radioimmunoassay methods; insulin by the coat-a-count procedure (Diagnostic Products Corporation, Los Angeles, CA); C-peptide using RIA-mat C-peptide II kit (BYK-Sangtec Diagnostica, Dietzenbach, RFA). For all tests, standard quality assurance procedures were employed.

Statistical Analysis

Paired comparisons were made within each subject to evaluate differences in profile areas across the three meals and in the glycemic indices between DM and SBF. These comparisons were conducted across all subjects and within subgroups defined by age, BMI and the phases of the menstrual cycle.

Descriptive statistics are given as the mean $\pm$ standard error throughout the text.

TABLE 1. Values (mean $\pm$ SEM) for areas under glucose, insulin and C-peptide curves in response to ingestion of isocaloric (300 calories) glucose solution, date meal and an urban Saudi breakfast in 19 normal Saudi patients.

	OGTT	DM	SBF
Mean G area $\pm$ SE (mmol/L $\times$ 180 min)	232.1 $\pm$ 31.0	118.67* $\pm$ 15.67	91.55* $\pm$ 12.55
Mean I area $\pm$ SE (pmol/L $\times$ 180 min)	51057.14 $\pm$ 8242.85	22642.86* $\pm$ 3185.71	25285.71* $\pm$ 4221.43
Mean C area $\pm$ SE (nmol/L $\times$ 180 min)	188.41 $\pm$ 13.90	106.29* $\pm$ 11.26	97.02* $\pm$ 7.61
GI	—	57.7** $\pm$ 8.55	79**

*P = < 0.05 (compared with OGTT) based on a parametric and nonparametric analysis.

**P = < 0.05 (parametric analysis).

Results

Table 1 shows the mean G, I and C areas for OGTT, DM and SBF and also the glycemic indices for DM and SBF. G, I and C areas were not different between DM and SBF but were when compared with OGTT ($P = < 0.05$). The GI for DM was computed individually for each of the 19 subjects and it ranged from 8.4–134.6. The average value for dates was 57.7 ± 8.5 which was significantly lower than the GI for SBF which was 79.0 ($P = < 0.05$). There were no differences detected with subgroups defined by age, BMI and the phases of the menstrual cycle.

Discussion

For thousands of years the date fruit has been the basis of life for the dwellers of the arid lands of Saudi Arabia. Over centuries, generations of Saudis have consumed large quantities of dates daily—a phenomenon rarely witnessed outside the middle eastern area. It is likely that such culturally acquired habits may have led to metabolic adaptations in this population. It is in this context that we decided to study only the Saudis (a population with well-primed date-eating habits), using an acute challenge of dates. Our observations, therefore, cannot necessarily be extrapolated to other populations.

Large quantities of dates of different varieties are harvested in different regions of Saudi Arabia. These differ in their color, taste and chemical composition [3]. It has been recognized that the chemical composition of dates is affected by different stages of maturity, changes during the ripening of dates naturally and at room temperature, changes during dehydration and during cold storage [8–10]. Our studies involved uniform use of only one variety of dates, "Khalas", harvested in a single season, administered to all subjects. This fruit is considered to be of an outstandingly high quality [4]. Palgrave referred to it as the date of perfection [11] and Fairchild described it as the most delicious date in the world [12].

Within specifications for harvesting, stage of maturity, ripening, processing, storage and thawing of the "Khalas" fruit used in our study, it is evident that the G, I and C profiles were similar between DM and SBF but were significantly lower

for each of these meals compared with OGTT. Contrary to the usual belief, this study refutes the suggestion that ingestion of dates adversely affects glucose tolerance compared with SBF in normal subjects. Similar results have been observed in preliminary studies in diabetic subjects in our laboratory (unpublished data).

In the last several years it has become evident that the plasma glucose and insulin responses to equal amounts of dietary CHO vary considerably depending on the specific food ingested [2,5]. These observations have led to the introduction of a classification of food items based on their "glycemic index" (GI). This information has been used to assign a relative ranking of plasma glucose responses to various CHO-containing foods. Similar values for the GI of CHO-containing foods have been found in both normal and diabetic subjects [13]. The ultimate purpose of this method of ranking plasma glucose responses with various foods is to assist the diabetic patients in meal planning. It has been suggested that the ingestion of foods of low GI could be beneficial in dietary management of diabetes [7].

Considering the relatively high prevalence of diabetes mellitus in the Kingdom of Saudi Arabia [14,15] and the culturally pivotal role of ingestion of dates, we considered it important to determine the GI of dates. This is the first documentation of GI for dates. For the "Khalas" variety it was found to be 57.7 ± 8.5 and was significantly lower than that for SBF, which was 79.0. These data together with the glucose and insulin profile areas document clearly that acute ingestion of dates does not adversely influence the glucose tolerance in normal Saudi individuals.

It is clear that future studies should be directed toward determination of glycemic indices in both normal and diabetic individuals, using different varieties of dates consumed in Saudi Arabia and other parts of the Middle East. Such studies should take into account the specific conditions for cultivation, harvesting, stage of maturation, processing and storage of the fruit—conditions shown to affect the chemical composition of the fruit [8–10] and likely to influence the values for

GI. Such studies are currently being pursued in our laboratory.

Acknowledgments

We acknowledge with great appreciation the cooperation of our volunteer subjects, the nursing staff on the metabolic unit, the nutritional assistance of Mr. Mohammed El-Yemni, the technical performance of the radioimmunoassay by Ms. Maureen Locke and the transcription assistance of Ms. Lorna Andrada and Ms. Maria Bernadette Martinez.

References

1. Wolever TMS, Nuttal FQ, Lee R, et al. Prediction of the relative blood glucose response of mixed meals using the white bread glycemic index. *Diabetes Care* 1985;8:418-28.
2. Crapo PA, Reaven G, Olefsky J. Post prandial plasma glucose and insulin responses to different complex carbohydrates. *Diabetes* 1977;26:1178-83.
3. Abdel Hafiz MJ, Shalabi AF, Al Akhal IAD. Chemical composition of 15 varieties of dates grown in Saudi Arabia. *Proc Saudi Biol Soc* 1980;4:181-93.
4. Hussein F, Elzeid AA. Chemical composition of "Khalas" dates grown in Saudi Arabia. *Egypt J Hort* 1975;2:209-14.
5. Jenkins DJA, Wolever TMS, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr* 1981;34:362-6.
6. Wolever TMS, Jenkins DJA. The use of the glycemic index in predicting the blood glucose response to mixed meals. *Am J Clin Nutr* 1986;43:167-72.
7. Jenkins DJA, Wolever TMS, Jenkins AL, et al. The glycemic response to carbohydrate foods. *Lancet* 1984;2:388-91.
8. Ashmawi H, Areef H, Hussein AEA. Compositional changes in Zaghloul dates throughout the different stages of maturity. *J Sci Food Agri* 1956;7:625-8.
9. Hussein F. Fruit growth and composition of two dry date cultivars grown at Asswan. *Top Agric Trin* 1970; 47:157-62.
10. Vinson AE, Freeman GF. Artificial ripening of dates. *Arizona Sta Bull* 1910;66:403-50.
11. Palgrave WG. "Personal narrative of a year's journey through Central and Eastern Arabia (1862-1863)". 1903;427. Illus London.
12. Fairchild DG. Persian Gulf dates and their introduction into Americas. *US Bur, Plant Industr Bull* 1093;54:32.
13. Jenkins DJA, Wolever TMS, Jenkins AL, et al. The glycemic index of foods tested in diabetic patients. A new basis for carbohydrate exchange favouring the use of legumes. *Diabetologia* 1983;24:257-64.
14. Bacchus RA, Bell JL, Madkour M, et al. The prevalence of diabetes mellitus in male Saudi Arabs. *Diabetologia* 1982;23:330-2.
15. Kingston M, Skoog WC. Diabetes in Saudi Arabia. *Saudi Med J* 1986;7(2):130-42.

LIPOID PROTEINOSIS: CLINICAL, GENETIC, AND PATHOLOGICAL STUDY OF A SAUDI ARABIAN FAMILY

Mirghani A. E. Uthman, MBBS, MSC, PhD;
Mohamed B. Satti, MBBS, MRCPATH;
Mohamed E. Baraka, MBBS, FRCS

نستعرض في هذه المقالة الملامح الشكلية والتطور السريري لداء البروتينات الشحمية لدى ستة مرضى من أسرة سعودية. تقدمت الحالة الدالة بشكوى بحة الصوت وآفات جلدية مميزة. أظهر بعض المرضى حساسية للضوء مع دخنيات وفرط الأشعار. وقد تم تأكيد الإصابة بداء البروتينات الشحمية بواسطة التشريح المرضي النسيجي مع وجود مستويات طبيعية من البورفيرين في الدم. هذه الحالة عبارة عن اضطراب وراثي جسمي صاغر تكون صلة القرى فيه عاملاً هاماً. إن ندرة هذه الحالة والتزاوج الشائع بين الأقارب في المملكة العربية السعودية دفعنا لكتابة هذا التقرير. ذلك أننا نعتقد أن هذه هي أول وأكبر أسرة تعاني من داء البروتينات الشحمية ويثبت انتماءها إلى سلالة عربية.

We present the morphological features and clinical progression of lipoid proteinosis observed in six patients from a Saudi family. The index case presented with hoarseness and characteristic skin lesions. Some of the patients had photosensitivity with milia and hypertrichosis. The diagnosis of lipoid proteinosis was confirmed by histopathology and by the finding of normal blood porphyrin levels. The condition is inherited as an autosomal recessive disorder, and consanguinity was an important factor. The rarity of this condition and the common occurrence of close-relative intermarriages in Saudi Arabia prompted this report, which we believe is the first and largest family with lipoid proteinosis possessing an established Arabian ancestry.

Lipoid proteinosis, also known as *hyalinosis cutis et mucosae*, is a rare autosomal recessive disorder characterized by deposition of homogeneous hyaline material in the skin and the mucosae of the head and neck region. The histochemical nature of the hyaline deposits has been demonstrated to be a glycoprotein. The presence of lipids, however, is not an essential feature [1]. The pathogenesis of the disease is unknown. Recent data, however, strongly suggest a perturbation of collagen metabolism with excessive production of matrix glycoproteins [2,3].

Approximately 250 cases of lipoid proteinosis

have been described in the literature, mostly in patients with a known European ancestry [4]. In this paper, we describe a Saudi Arabian family in which six of the offspring are affected by the disease. We describe the clinical features and genetic background of this rare condition to facilitate its diagnosis in an area of the world where consanguinity is common and is expected to contribute to an increased incidence of the disease.

Subjects and Results

Case Report

An 11-year-old boy (propositus in pedigree and number 3 in Tables 1 and 2) was the first patient seen with hoarseness and skin lesions that had existed since infancy. Examination revealed thickening of the skin and presence of pock-like scarring on the face. The free margins of his eyelids were thickened and beaded with tiny waxy papules (Figure 1). Atrophic scars and hyperpig-

From the Departments of Dermatology (Dr. Uthman), Pathology (Dr. Satti), and Surgery (ENT) (Dr. Baraka), College of Medicine and Medical Sciences, King Faisal University, Dammam.

Address reprint requests and correspondence to Dr. Uthman: College of Medicine and Medical Sciences, King Faisal University, P.O. Box 2114, Dammam 31451, Saudi Arabia.

Accepted for publication 4 September 1990.



FIGURE 1. Pock-like scarring of the skin of the face with thickening and beading of the eyelid.

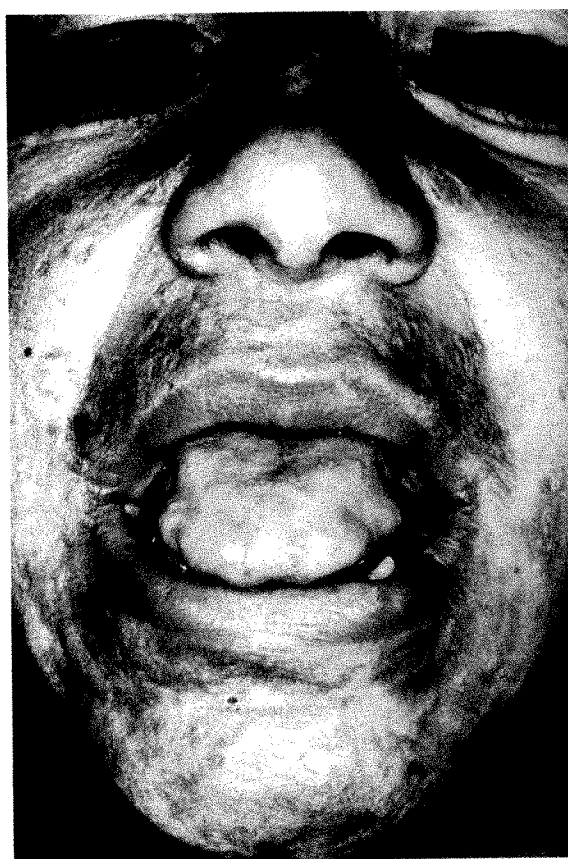


FIGURE 2. Woody tongue with thickened plaques and irregular margins.

mented verrucoid plaques were present in the limbs and particularly on the elbows and knees. The tongue was thickened with pale yellowish plaques and its margins were irregular (Figure 2). Its mobility was restricted and it appeared to be stuck to the floor of the mouth. The mucosae of the lips, soft palate, and palatoglossal folds showed irregular thickening and similar yellowish plaques. Laryngeal examination using indirect laryngoscopy was practically impossible to perform due to difficulty in tongue protrusion. However, microlaryngoscopic examination revealed white to yellow plaques on the laryngeal mucosae, and the margins of the true vocal cords were thickened and nodular. A clinical diagnosis of lipoid proteinosis was made and confirmed by skin and laryngeal biopsies.

Family Report

Family history and examination showed that the parents were first cousins and did not exhibit

any features of the disease. The younger sister of the patient, aged 4 years, had a mild degree of hoarseness, subtle infiltrated plaques on her tongue, and vesiculopustular skin lesions on her nose (Figure 3). Similar skin lesions with milia formation were more florid and crusted on the elbows, knees, and hands of the patient (Figure 4). Subsequent examination of other family members revealed that four of the first cousins were affected by the disease (Figure 5). They were all evaluated; their symptoms are summarized in Table 1 and the clinical findings are shown in Table 2.

The presenting features in all patients were hoarseness, mucosal plaques, and skin lesions. The voice abnormality was noticed in infancy as a weak-cry. During childhood the voice became progressively husky and low pitched. At adolescence the degree of hoarseness varied from patient to patient but remained unchanged afterwards. Microlaryngoscopic examination revealed

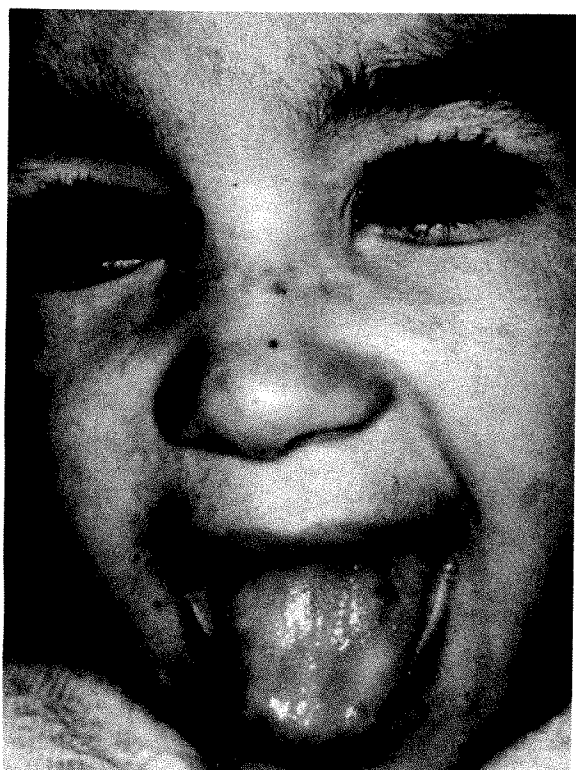


FIGURE 3. Waxy infiltration of the skin of the face, subtle pale plaques on the tongue, and hypertrichosis.



FIGURE 4. Early vesiculopustular lesions with milia formation on the skin of hands.

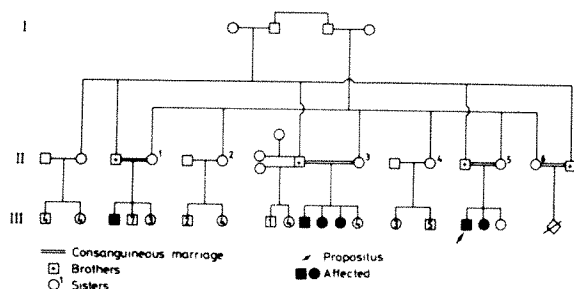


FIGURE 5. Pedigree of the Saudi family with lipoid proteinosis.

TABLE 1. Lipoid proteinosis in a Saudi family: summary of history and symptoms.

Case no.	Age(yr) Sex	Hoarse- ness	Dys- phagia	Skin lesions	Dysp- nea	Neurological deficit
1	4,F	+	-	-	-	-
2	5,F	+	-	+	-	-
3	11,M	+++	+	+++	-	+
4	18,M	++	-	+	-	-
5	20,F	++	-	+++	-	-
6	25,M	+++	+	+	-	+++

+ = mild; ++ = moderate; +++ = severe; - = none.

TABLE 2. Lipoid proteinosis in a Saudi family: summary of clinical findings.

	Case number					
	1	2	3	4	5	6
<i>Skin lesions</i>						
Keratotic plaques	-	-	+++	+	++	+
Beading of eyelids	-	-	+++	+	+++	++
Blisters and pustules	+	+	+	+	+	+
Varioliform scars	-	+	+++	+	+	++
Alopecia	-	-	-	-	-	-
Nail and teeth	-	-	+	-	-	-
Photosensitivity	+	-	++	-	-	+
Milia and hypertrichosis	+	-	++	-	-	+
<i>Mucosal lesions</i>						
Tongue	+	+	+++	+	++	++
Lips	-	-	+	-	-	+
Soft palate	-	-	++	+	+	++
Larynx	-	-	+++	+	+	++
<i>Intracranial calcification</i>						
Skull x-ray studies	-	-	-	-	-	-
CT scan	-	-	+	-	-	++

+ = mild; ++ = moderate; +++ = severe; - = none.

the presence of mucosal thickening and plaques in four patients and limited movements of the true vocal cords in two. The skin lesions resembled superficial infections and healed spontaneously with varioliform scarring. They were seen on sun-exposed areas and sites of friction. The characteristic "string-of-beads" appearance along the eyelid margins (Figure 6) was present in four patients. Mild to moderate photosensitivity was manifested as macular erythema, and burning sensation following sun exposure was noted in three patients. Careful examination of these photosensitive patients revealed the presence of

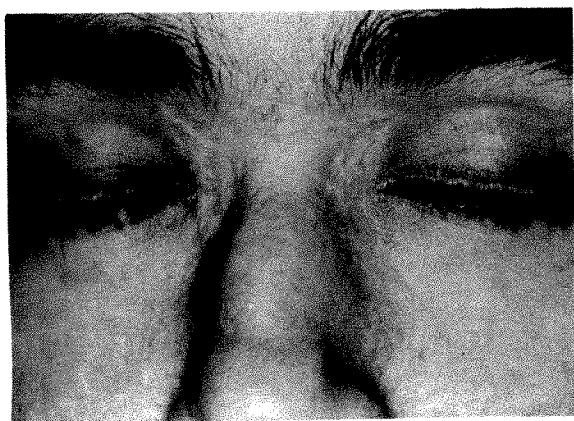


FIGURE 6. The characteristic and pathognomonic "string of beads" of the eyelids.

hypertrichosis and milia. The possibility of porphyria was ruled out in these patients by the finding of normal porphyrin levels in urine, feces, and blood. Serum immunoglobulins, antinuclear antibody, and human lymphocyte antigen studies were not done since there was no clinical evidence suggesting other photosensitivity syndromes.

All laboratory investigations done, including urinalysis, hematological indices, fasting blood sugar, blood lipids, lipoproteins, urea, creatinine, electrolytes, and transaminases, were found to be within normal values in all patients. Plain skull radiographs were normal in all patients, but computed tomographic (CT) scan demonstrated the presence of intracranial calcifications in the region of the hippocampus in two patients. One of these patients had a low intelligence and a poor memory, while the other was mentally handicapped with aggressive behavior and epilepsy since childhood.

Histopathology. Punch biopsies from skin lesions of three patients showed an identical and characteristic homogeneous mantle of periodic-acid-Schiff (PAS)-positive hyaline deposits in the papillary dermis (Figure 7). In the deep reticular dermis, the deposits surrounded the sweat glands and their ducts (Figure 8). The epidermis showed variable hyperkeratosis, acanthosis, and papillomatosis. Laryngeal biopsies taken from two patients by microlaryngoscopy showed the presence of similar PAS-positive deposits in the subepithelial connective tissue. In combination with the clinical background, these histopathological features were diagnostic of lipid proteinosis.

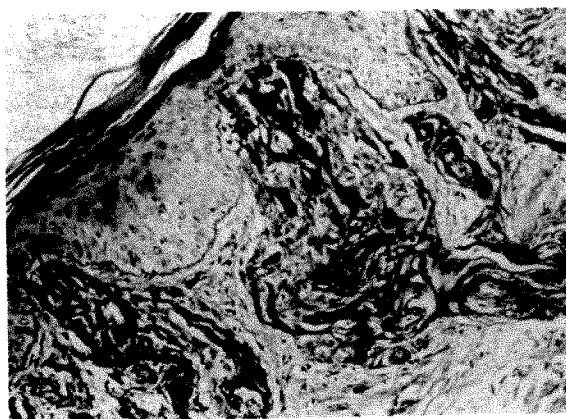


FIGURE 7. Heave deposits of periodic-acid-Schiff (PAS)-positive hyaline material in the papillary dermis. (Periodic-acid-Schiff, original magnification, $\times 150$.)

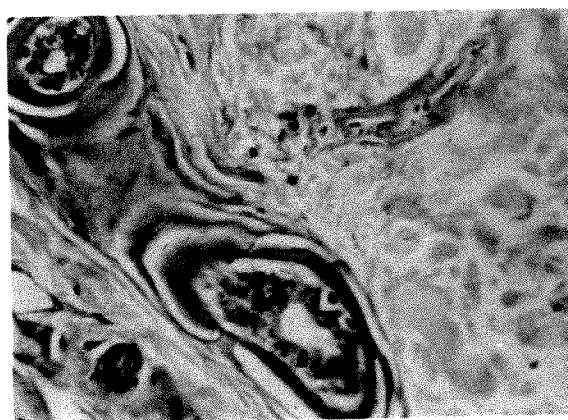


FIGURE 8. Hyaline deposits around sweat gland ducts in the deep dermis. (Periodic-acid-Schiff, original magnification, $\times 325$.)

Discussion

Lipoid proteinosis is inherited as a monogenetic autosomal recessive disorder with normal chromosomes and showing equal sex distribution [4,5]. The family pedigree of our patients showed features characteristic of an autosomal recessive mode of inheritance and furthermore demonstrated clearly the influence of parental consanguinity in the expression of the disease in offspring (Figure 5). Consanguinity has been reported in 20% of the patients with lipid proteinosis [5], but the gene frequency may rise considerably in a population where intermarriages are common [6]. Most of the reported cases of lipid proteinosis have been traced to German or Dutch origin [5,6]. The only reported cases from

the Middle East have been in Egyptians [7,8], but familial and genetic studies to trace these patients were not done. We believe that our report of this Saudi family is the first in patients with a known Arabian ancestry.

The evolution of lipoid proteinosis in our patients appears to be similar. The clinical features, however, presented a wide spectrum due to variation in both severity and stage of the disease. Mucosal signs were present since infancy, and active progression of the disease with skin scarring occurred during childhood. The disease tended to stabilize toward adolescence.

The earliest and most typical symptom of lipoid proteinosis is hoarseness [4], and in its absence the diagnosis has been considered to be doubtful [9]. Hoarseness during childhood was present in all our patients and is thought to be due to progressive infiltration and thickening of the true vocal cords [10]. Microlaryngoscopic examination demonstrated thickened nodularities of the true vocal cords in four of our patients, and limited mobility of the true vocal cords was also evident in two patients with severe hoarseness. Mucosal involvement is best observed in the tongue, which assumes a "woody" consistency and restricted mobility. Mucosal plaques in the mouth and pharynx may be subtle or pale white, and thus may be mistaken for leukoplakia [11]. In lipoid proteinosis, systemic lesions have been reported in the gastrointestinal tract, respiratory tract [12], and in organs such as the lungs, lymph nodes, kidneys, pancreas, testes, and brain [4]. We were unable to detect any systemic involvement in our patients.

Intracerebral deposits and calcification of the hippocampal region have been noted frequently during x-ray examination in patients with lipoid proteinosis [13,14]. Skull x-ray studies of our patients were negative, but CT scans were more sensitive in demonstrating the presence of brain calcification in two patients and showed characteristics similar to those described by others [15,16]. The presence of intracerebral calcification has been held responsible for the occurrence of convulsive seizures [17], but we were unable to relate them to the existing neurological deficits in the two patients with such calcification.

Our observation that the primary skin lesions were vesiculopustular and localized to the sun-

exposed areas or sites of friction have been noted by a few authors [18,19]. They have been related to fragility and weakness of the skin due to deposition of the hyaline material at the dermal-epidermal junction [20]. The presence of photosensitivity in three of our patients (Table 2) strongly supports the existence of a "light sensitive" type of lipoid proteinosis [20]. We agree that such patients can be confused with patients who have erythropoietic protoporphyria, and on both clinical and histopathological grounds [21]. The presence of milia and hypertrichosis in these photosensitive patients is a further source of confusion with erythropoietic protoporphyria. The findings of normal levels of erythrocyte porphyrins in our patients, however, confirmed the diagnosis.

Lipoid proteinosis is a chronic but relatively benign disease. Treatment of our patients was symptomatic and conservative, and none of our patients needed surgical intervention for severe dysphagia or dyspnea. The recently reported favorable response of lipoid proteinosis to dimethylsulfoxide [22] and its safety are encouraging, as there is no available treatment for this disease.

References

1. Shore RN, Howard BV, Howard WJ, et al. Lipoid proteinosis: demonstration of normal lipid metabolism in cultured cells. *Arch Dermatol* 1974;110:591-4.
2. Harper JJ, Duance VC, Sims TJ, et al. Lipoid proteinosis: an inherited disorder of collagen metabolism? *Br J Dermatol* 1985;113:145-51.
3. Fleischmajer R, Kneg T, Dziadek M, et al. Ultrastructure and composition of connective tissue in hyalinos cutis et mucosae skin. *J Invest Dermatol* 1984;82:252.
4. Hofer PA. Urbach-Wiethe disease: a review. *Acta Dermatol Venereol (Stockh)* 1973;53(suppl 71):1-52.
5. Hofer PA. Urbach-Wiethe disease: a clinico-genetic study of 14 families from northern Sweden. *Hereditas* 1974;77:209-18.
6. Meenan FOC, Bowe SD, Dinn JJ, et al. Lipoid proteinosis: a clinical, pathological and genetic study. *Q J Med* 1978;47:549-61.
7. El-Barbery A, Yassin A, El-Shennawy M. Lipoid proteinosis. *J Laryngol Otol* 1971;85:505-10.
8. Aziz MT, Mandour MA, El-Gazzawi IF, et al. Urbach-Wiethe disease in ORL practice. *J Laryngol Otol* 1980;94:1309-19.
9. Grosfeld JCM, Spaas J, Van De Staak WJBM, et al. Hyalinos cutis et mucosae. *Dermatologica* 1965;130:239-66.
10. Harper JJ, Duguid KP, Staughton RCD, et al. Oropharyngeal and laryngeal lesions in lipoid proteinosis. *J Laryngol Otol* 1983;97:877-82.

11. Simpson HE. Oral manifestations in lipoid proteinosis. *Oral Surg* 1972;33:528-32.
12. Caplan RM. Visceral involvement in lipoid proteinosis. *Arch Dermatol* 1967;95:149-55.
13. Weidner WA, Wenzel JE, Swischuck LE. Roentgenographic findings in lipoid proteinosis. *Am J Roentgenol* 1970;110:457-61.
14. Francis RS. Lipoid proteinosis. *Radiology* 1975;117:301-2.
15. Singh G, Misra D. Lipoid proteinosis. *Int J Dermatol* 1988;27:344-5.
16. Leonard JN, Ryan TJ, Sheldon PWE. CT scan appearance in a patient with lipoid proteinosis. *Br J Radiol* 1981;54:1098-100.
17. Laymon CW, Hiu EM. An appraisal of hyaline cutis et mucosae. *Arch Dermatol* 1957;75:55-65.
18. Caro I. Lipoid proteinosis. *Int J Dermatol* 1978;17:388-93.
19. Findlay GH. Hyalinosis cutis et mucosae. *S Afr Med J* 1960;34:189-95.
20. Findlay GH. Lipoid proteinosis. In: Fitzpatrick T, Eisen AZ, Wolff K, et al, (eds). *Dermatology in general medicine*, 3rd ed. New York: McGraw-Hill 1987;1760-3.
21. Van Der Walt JJ, Heyl T. Lipoid proteinosis and erythropoietic protoporphyria. *Arch Dermatol* 1971;104:501-7.
22. Wong CK, Lin CS. Remarkable response of lipoid proteinosis to oral dimethyl sulphoxide. *Br J Dermatol* 1988;119:541-4.

USE OF GAS LIQUID CHROMATOGRAPHY AS AN ADJUNCT TO CONVENTIONAL BACTERIOLOGICAL METHODS IN THE DIAGNOSIS OF ANAEROBIC CEREBRAL ABSCESS

Sabiha Pit, MD, MSc; Farida Jamal, MBBS, MSc, MRCPPath;
Fadzli K. Cheah, MBBS, FRCS(Edin); Mohammed Ariff Mohammed Abbas, MLT

تمت دراسة استطلاعية على أربعين حالة متتالية من الخراج المخي لاثبات العوامل الجرثومية المسؤولة عن تلك الحالات. كان من أكثر العوامل المؤهبة توارداً للتهاب المزمن في الأذن الوسطى (١٤ مريضاً، ٣٥٪)، والداء الخلقي في القلب (٥ مريضاً، ١٢،٥٪) والتهاب السحايا (٥ مريضاً، ١٢،٥٪). كانت العدديات أكثر ما عزل من العوامل المسببة (١٤ مريضاً، ٣٥٪) وكان النوع الغالب منها العقدية الممرية (١١ مريضاً، ٢٧،٥٪). شملت العضويات الأخرى التي تم عزلها المتقلبات الرائعة في ستة مريضاً (١٥٪) والعنقوديات الذهبية في خمسة مريضاً (١٢،٥٪). أدت اللاهوائيات (١٢ مريضاً، ٣٠٪) وبخاصة العصوانيات (ثمانية مريضاً، ٢٠٪) دوراً مهماً في تلك الحالات، وتم عزل معظمها من مزارع مختلطة. أظهر فحص القيح بالاستشراب الغازي السائل وجود اللاهوائيات في إحدى عشرة حالة أخرى من الخراج المخي حين كانت مزارعها اللاهوائية سلبية. لذا فإن الاستشراب الغازي السائل يعتبر إضافة مفيدة للطرق التقليدية في كشف الجراثيم، وذلك بتوفيره طريقة سريعة وحساسة للكشف عن اللاهوائيات في القيح وبخاصة ذلك المأخوذ من المرضى الذين تلقوا مضادات حيوية قبل دخول المستشفى.

Forty cases of cerebral abscesses were studied prospectively to establish the microbial agents implicated in these cases. Chronic otitis media (14 patients, 35%), congenital heart disease (five patients, 12.5%), and meningitis (five patients, 12.5%) were among the important predisposing factors. *Streptococcus* (14 patients, 35%) was the most common causative agent isolated, the predominant species being *Streptococcus milleri* (11 patients, 27.5%). Other organisms isolated included *Proteus mirabilis* in six patients (15%) and *Staphylococcus aureus* in five patients (12.5%). Anaerobes (12 patients, 30%), predominantly *Bacteroides* sp. (eight patients, 20%), played an important role in these cases, the majority of which were isolated in mixed cultures. Gas-liquid chromatographic analysis of pus detected the presence of anaerobes in another 11 cases of cerebral abscess, in which cultures for anaerobes were negative. Therefore, gas-liquid chromatography is useful as an adjunct to conventional bacteriological methods in providing a rapid and sensitive means of detecting anaerobes in pus obtained especially from patients who had received antibiotic therapy prior to hospitalization.

From the Department of Microbiology (Drs. Pit and Jamal and Mr. Abbas) and Neurosurgical Unit, Department of Surgery (Dr. Cheah), Faculty of Medicine, National University of Malaysia, Kuala Lumpur, West Malaysia.

Address reprint requests and correspondence to Dr. Pit: Department of Microbiology, Faculty of Medicine, National University of Malaysia, Jalan Raja Muda Aziz, 50300 Kuala Lumpur, West Malaysia.

Accepted for publication 22 August 1990.

Early diagnosis and immediate treatment of cerebral abscess are of utmost importance. Early intervention by drainage and administration of antibiotics reduce the resulting morbidity and mortality. Rational use of antibiotics depends on knowledge of the microbial causes of cerebral abscess. Although the site of origin of the abscesses may indicate the likely microorganisms pres-

ent, this is often unclear. In a study by De Louvois et al [1], streptococci were found to be the most common organisms isolated. Enterobacteriaceae and the *Bacteroides* group were isolated in mixed cultures, especially in cases secondary to otitis media [1]. Other studies have also shown that anaerobes were commonly encountered in cerebral pus [2-5].

Apart from retrospective review of medical records [6,7], little published data are available from developing countries on the topic of the microbiology of brain abscess [5]. To the best of our knowledge, this is the first documented prospective study carried out to establish the etiology of cerebral abscess in Malaysia, and also to assess the usefulness of gas-liquid chromatography as an adjunct to conventional bacteriological methods in the rapid diagnosis of anaerobic cerebral abscess.

Material and Methods

Forty patients were referred to the Neurosurgical Unit, Department of Surgery, Medical Faculty, National University of Malaysia, from January 1987 to December 1988. Following computerized tomographic scanning to locate the abscess, pus was aspirated by an emergency burrhole operation. Either a microbiologist or laboratory personnel attended the operating sessions in the theatre to ensure immediate collection of specimens. Pus specimens were collected into plain sterile bottles and were also inoculated into thioglycollate broth and Robertson's cooked meat media in the operating theatre without further delay. These specimens of pus were then processed in the Diagnostic Bacteriology Laboratory, Microbiology Department, National University of Malaysia.

Bacteriological Studies

Specimens of pus received were processed within half an hour of collection from the operating theatre. The specimens were examined by direct microscopy of Gram-stained smears and were also wet mount to look for the presence of protozoa. These specimens were inoculated onto blood agar plates, which were incubated aerobically onto prereduced anaerobic blood agar (supplemented with 1% kanamycin, vitamin K, and hemin) and additional blood agar plates, which

were incubated anaerobically with added 10% carbon dioxide. Anaerobic blood agar plates were pre-reduced by incubating the uninoculated plates in anaerobic jars for 18 to 24 hours before using them. The specimens were also inoculated onto chocolate agar, incubated in 10% carbon dioxide, and also onto MacConkey agar, incubated aerobically.

All plates were examined after 24 to 48 hours and were incubated for at least 5 days before discarding them. Subcultures were made from thioglycollate and Robertson's cooked meat after preliminary incubation at $37 \pm C$ for 48 hours' incubation on plates, as described above, and were similarly incubated. The organisms isolated were identified according to the taxonomic criteria of Cowan and Steel [8]. Streptococci were identified according to the methods of Facklam [9] and with API Strept Kits. Anaerobes were identified on the basis of their Gram-stain and antibiotic susceptibility pattern (An-Ident Disc, Oxoid). A BBL Gaspak system was used for anaerobic incubation. The catalysts were changed once a month. An anaerobic indicator (BBL strip) was used as a control of anaerobiosis.

The initial antibiotic regimen used in this study consisted of ampicillin, cloxacillin, and chloramphenicol with the aim of covering the streptococci and enterococci, staphylococci, and the Gram-negative organisms as well as the anaerobes, respectively. Antibiotic susceptibility testing of isolates was carried out using the disc diffusion technique on a Diagnostic Sensitivity test agar (Oxoid) by the comparative methods [10]. Penicillin, ampicillin, chloramphenicol, cloxacillin, and metronidazole were routinely tested; newer cephalosporins were included whenever necessary.

Gas-liquid Chromatography

A 5730A Hewlett Packard chromatograph equipped with a flame ionization detector was used for the analysis of volatile fatty acids from the specimens. The column used was SP 1220 15% and nitrogen was the carrier gas. A 3380A integrator, connected to the chromatograph, was used to produce the trace of acid peaks detected.

Analysis of Volatile Fatty Acids

One microliter of each sample of pus was

acidified with a few drops of 50% sulfuric acid, and volatile fatty acids were extracted in one milliliter of diethyl ether. One microliter of the ether layer was withdrawn and injected into the chromatograph. A standard volatile fatty acid solution was chromatographed at the same time, and the acid peaks detected in the specimen were then compared. The standard volatile fatty acid solution contained approximately 1 mEq/dl of each of the following acids: acetic, propionic, isobutyric, butyric, isovaleric, valeric, isocaproic, caproic, and haptanoic [11].

Results

Chronic otitis media was the most common predisposing factor (14 patients, 35%) associated with brain abscess, followed by meningitis (five patients, 12.5%) and congenital heart disease (five patients, 12.5%). In seven patients (17.5%), no predisposing factors were identified and most presented with acute onset of neurological symptoms (Table 1).

Pure cultures predominated over mixed cultures, and sterile cultures were obtained only in three patients (7.5%). Organisms that were isolated from these 40 cases of cerebral abscess are summarized in Table 2. *Streptococcus milleri* (27.5%) was the most common organism isolated, followed by *Bacteroides* sp. (20%), *Proteus* sp. (15%), and *Staphylococcus aureus* (12.5%). Most of the *Streptococcus milleri* were isolated in pure

cultures, whereas the *Bacteroides* sp. organisms were isolated predominantly in mixed cultures.

Table 3 shows a comparison of the sensitivity and specificity of gas-liquid chromatography versus those of the culture results. Gas-liquid chromatography showed a sensitivity of 91.7% and specificity of 60.7%, compared with those of the cultures (sensitivity of 50%, specificity of 94.4%) in detecting anaerobes. Table 4 shows the smear and culture results from 11 cases of cerebral abscess in which anaerobes were detected only by gas-liquid chromatography. In the majority of these cases, organisms were detected in Gram-stained smears, although cultures for anaerobes were negative.

TABLE 2. Distribution of causative microorganisms isolated from cerebral abscesses.

Microorganisms	Pure	Mixed	Total	%
<i>Staphylococcus aureus</i>	5	0	5	12.5
<i>Staphylococcus epidermidis</i>	2	0	2	5.0
<i>Streptococcus agalactiae</i>	1	0	1	2.5
<i>Streptococcus milleri</i>	8	3	11	27.5
<i>Streptococcus mitis</i>	1	0	1	2.5
<i>Enterococcus avium</i>	0	1	1	2.5
<i>Proteus mirabilis</i>	3	3	6	15.0
<i>Salmonella stanley</i>	1	0	1	2.5
<i>Moraxella</i> sp.	0	1	1	2.5
<i>Klebsiella</i> sp.	0	1	1	2.5
<i>Pseudomonas aeruginosa</i>	0	1	1	2.5
<i>Pseudomonas pseudomallei</i>	1	0	1	2.5
<i>Bacteroides</i> sp.	1	7	8	20.0
<i>Fusobacterium</i> sp.	1	0	1	2.5
<i>Propionibacterium</i> sp.	1	0	1	2.5
Anaerobic cocci	1	1	2	5.0

TABLE 1. Predisposing factors in 40 cases of cerebral abscesses.

Predisposing factors	No. (%)
Chronic otitis media	14 (35.0)
Congenital heart disease	5 (12.5)
Meningitis	5 (12.5)
Post head trauma	2 (5.0)
Chronic sinusitis	1 (2.5)
Bronchiectasis	1 (2.5)
Dental caries	1 (2.5)
Orbital infection	1 (2.5)
Mainliner drug addict	1 (2.5)
Multiple scalp abscesses	1 (2.5)
Pineal gland tumor with shunt	1 (2.5)
Unknown	7 (17.5)
Total	40

TABLE 3. Comparison between conventional bacteriological techniques and gas-liquid chromatography in detection of anaerobes.^a

GLC	Culture		Total
	Positive	Negative	
Presence of volatile fatty acids	11	11	22
Absence of volatile fatty acids	1	17	18
Total	12	28	40

^a Based on the above figures: specificity of GLC, 60.7%; sensitivity of GLC, 91.7%.

GLC = gas-liquid chromatography.

TABLE 4. Smears and cultures for 11 cases of cerebral abscess where anaerobes were detected only by gas-liquid chromatography.

Smear	Cultures	No. of cases
Gram-positive cocci	<i>Streptococcus milleri</i>	3
Gram-positive cocci	<i>Staphylococcus aureus</i>	1
Gram-positive cocci	No growth	1
Gram-positive cocci & gram-negative rods	<i>Proteus mirabilis</i>	2
Gram-positive cocci & gram-negative rods	<i>Proteus mirabilis</i> & <i>Streptococcus milleri</i>	1
Gram-positive cocci & gram-negative rods	<i>Salmonella stanley</i>	1
Gram-positive cocci & gram-negative rods	<i>Streptococcus milleri</i>	2

Discussion

It is very important to establish the nature of infection in cases of cerebral abscess, as these patients require immediate appropriate antimicrobial therapy. Evidence of antecedent infections was found in 33 of 40 (82.5%) cases. Chronic otitis media (14 patients, 35%) was the most common predisposing factor associated with cerebral abscess. Congenital heart disease (five patients, 12.5%) and meningitis (five patients, 12.5%) were among other common and important predisposing factors associated with these cases.

In our study of 40 cases of cerebral abscess, *Streptococcus milleri* (27.5%) was the most common organism isolated and anaerobes played an important role. These findings are similar to those reported elsewhere [1]. Positive cultures were obtained in 37 (92.5%) cases, and sterile cultures were seen in three (7.5%) cases. Pure cultures predominated over mixed cultures; most of the mixed cultures grew organisms that were members of the Enterobacteriaceae family or were anaerobes. Historically, the incidence of so-called sterile pus was much higher before adequate anaerobic techniques were available and before the role of anaerobes as causative agents of cerebral abscess was established.

Even as late as 1963, Heineman and Braude [12] had failed to isolate obligate anaerobes in their study. Due to the fastidious nature of

anaerobes, and the need of special selective media, prompt inoculation of specimens to the culture plates and prompt incubation in anaerobic atmosphere are mandatory to ensure their isolation. Certain precautions were taken in our study to ensure maximum isolation of anaerobes. Despite these attempts, anaerobes were isolated in only 12 patients (30.0%).

Phillips et al [13] used gas-liquid chromatography for rapid presumptive differentiation of anaerobic from aerobic infections. In the present study, gas-liquid chromatography showed a sensitivity of 91.7% and a specificity of 60.7%. The presence of anaerobes was based on the presence of volatile fatty acids, but the amounts of volatile fatty acids produced were not quantitated. Acetic acid and sometimes propionic acid were the only volatile fatty acids found in the gas-liquid chromatographic profiles of certain species of *Peptostreptococcus* and *Veillonella* sp. [11] and that of *Streptococcus milleri*. In addition, acetic acid was the only volatile fatty acid produced by certain species of *Peptococcus* [11] and some facultative anaerobes. Gas-liquid chromatographic volatile fatty acid profiles were not sufficiently distinct to differentiate between peptococci and peptostreptococci, and also the facultative anaerobes. This explained its low specificity (60.7%) in detecting anaerobes. On the contrary, the chromatographic analysis of pus in our study detected anaerobes in another 11 cases of cerebral abscess, in which anaerobes were not isolated on cultures. Similar results were also obtained in other reports [14,15]. Thus, these findings confirmed those of other studies showing that gas-liquid chromatography is useful as an adjunct to the conventional bacteriological method, in providing a rapid and sensitive means of detecting anaerobes even in pus from patients who had received prior antibiotic therapy. In centers where facilities for gas-liquid chromatography are available, an early report on the Gram-stained smears together with the gas-liquid chromatographic analysis of volatile fatty acids of pus may provide useful therapeutic information, and the neurosurgeon should be informed of these as soon as possible. Initial antimicrobial therapy may have to be modified once the final reports of cultures and sensitivities are available.

Acknowledgment

The Project was funded by National University of Malaysia, Grant No. 48/85.

References

1. De Louvois J, Gortvai P, Hurley R. Bacteriology of abscesses of central nervous system—a multicentre prospective study. *Br Med J* 1977;2:981-4.
2. Andrew G, Adrian DL. Role of anaerobes in cerebral abscesses of sinus origin. *Br Med J* 1984;288:758-9.
3. Ariza J, Casanova A, Fernandez VP, et al. Etiological agent and primary source of infection in 42 cases of focal intracranial suppuration. *J Clin Microbiol* 1986;24(5):899-902.
4. Schliamser SE, Backman K, Norrby SR. Intracranial abscesses in adults: an analysis of 54 consecutive cases. *Scand J Infect Dis* 1988;20:1-9.
5. Bharadwaj R, Joshi BN. Brain abscesses—a study of the causative organisms with special reference to anaerobes. *Indian J Pathol Microbiol* 1988;32(2):44-8.
6. Clezy JKA. Brain abscess—then and now. *PNG Med J* 1985;28:115-7.
7. Snyman H, Kruger P, Van Den Heever CM. Intracranial sepsis. *S Afr J Surg* 1986;24:78-80.
8. Cowan ST, Steel KJ. Manual for the identification of medical bacteria, ed 2. Cambridge: Cambridge University Press, 1975.
9. Facklam RR. Physiological differentiation of viridans streptococci. *J Clin Microbiol* 1977;52:184-201.
10. Garrod LP, Lambert HP, O'Grady F. Antibiotic and chemotherapy, ed 5. Edinburgh: Churchill Livingstone, 1981;464-504.
11. Holdeman LV, Cato EP, Moore WEC. Anaerobe Laboratory Manual, ed 4. Blacksburg, VA: Virginia Polytechnic Institute and State University, 1977.
12. Heineman HS, Braude AI. Anaerobic infection of brain. *Am J Med* 1963;35:682-7.
13. Phillips KD, Tearle PV, Willis AT. Rapid diagnosis of anaerobic infection by gas liquid chromatography of clinical specimens. *J Clin Pathol* 1976;29:428-32.
14. Gupta U, Murugesan K, Bhatia R, et al. Gas liquid chromatography in rapid diagnosis of anaerobic brain abscess. *Indian J Med Res* 1986;84:502-7.
15. Galloway A, Green T. Short report. *Br Med J* 1984;288:1086.

BACTERIURIA, INCIDENCE, CAUSATIVE MICROORGANISM, AND SUSCEPTIBILITY PATTERN AT QATIF CENTRAL HOSPITAL

Ali Magzoub El-Bashier, MRCPATH

جمعنا ١٣,١٩٣ عينة بولية من المرضى النوميين والمراجعين لمستشفى القطيف المركزي الواقع في شرق المملكة العربية السعودية خلال الفترة من شهر أغسطس ١٩٨٨ إلى شهر يناير ١٩٩٠م لتحديد نسبة وقوع بيلة جرثومية هامة، والأحياء الدقيقة المسببة لها ومدى عنونها لمضادات الجراثيم. أظهرت ١٠٠٤ عينة (٧,٦٪) بيلة جرثومية هامة. كانت نسبة الانتشار في حالات البيلة الجرثومية المكتسبة في المجتمع أكبر لدى الإناث منها لدى الذكور. وكانت الأشريكية القولونية وأنواع الكلبسيلا والمعوية غالبية فيما تم عزله. أظهرت اختبارات العنوا لمضادات الجراثيم مقاومة للأمبيسلين، وعليه فإننا نقترح التفكير باستخدام النورفلوكساسين في المعالجة التخيرية، وخصوصاً في حالات الاشتباه بأخماج السيل البولي بالزوائد. هذا ومن المهم التمييز بين الاستيطان والحمج، لدى من يحملون قثطرة ثابتة، قبل البدء بالمعالجة المضادة للجراثيم. إن الصعوبات في معالجة أخماج السيل البولي لدى حاملي القثطرة الثابتة تؤكد مدى أهمية الإجراءات الوقائية.

From August 1988 to January 1990, a total of 13,193 urine specimens were collected from inpatients and outpatients of Qatif Central Hospital, located in the Eastern Province of Saudi Arabia, to determine the incidence of significant bacteriuria, causative microorganisms, and antimicrobial susceptibility. Among these, 1004 specimens (7.6%) showed significant bacteriuria. In community-acquired cases of bacteriuria, the prevalence was greater in female than in male patients. The most common organisms isolated were *Escherichia coli* and *Klebsiella-Enterobacter* species. Antimicrobial susceptibility showed high resistance to ampicillin, and therefore we suggest that norfloxacin be considered in empirical therapy, particularly in suspected cases of *Pseudomonas* urinary tract infections. For patients with an indwelling catheter, it is important to differentiate between colonization and infection before initiating antimicrobial therapy. The difficulties in treating urinary tract infections in patients with an indwelling catheter emphasize the importance of preventive measures.

The urinary tract is the most common site of all serious bacterial infections [1]. It has been estimated that urinary tract infections account for approximately 40% of all hospital-acquired infections [2], and that 75% of all patients with nosocomial urinary tract infections have a history of urological instrumentation, usually catheterization [3]. It has also been documented that catheter-associated urinary tract infections are a major antecedent of gram-negative septicemia, a poten-

tially serious condition with a mortality of 20 to 50% [4,5]. Prompt diagnosis, proper management, and prevention of bacteriuria can reduce the incidence of the life-threatening consequences of urinary tract infections. The aim of this study was to assess the incidence, causative organisms, and antibiotic susceptibilities of urinary tract infections at Qatif Central Hospital, a 400-bed hospital located in the Eastern Province of Saudi Arabia.

Material and Methods

Clean-catch midstream and catheter urine specimens from outpatients and inpatients were collected over a period of 18 months, from August 1988 through January 1990. Catheter specimens

From the Department of Microbiology, Qatif Central Hospital, Al-Jesh.

Address reprint requests and correspondence to Dr. El-Bashier: Department of Microbiology, Qatif Central Hospital, P.O. Box 18439, Al-Jesh 31911, Saudi Arabia.

Accepted for publication 22 August 1990.

were obtained by aspiration from the tube after cleaning with alcohol and clamping for approximately 15 minutes.

Specimens of urine were collected in a sterile universal container and transported to the microbiology laboratory within 30 minutes of collection. Specimens collected at night were kept refrigerated until morning and were processed within 30 minutes of arrival in the microbiology laboratory. All unspun well-mixed samples were examined microscopically for pus cells, casts, red cells and bacteria under a $\times 40$ objective and $\times 10$ eye piece. Three or more pus cells per field were considered indicative of pyuria.

Culture of urine and determination of significant bacterial count were performed by the semiquantitative method using the calibrated loop, direct-streak method [6]. The loops used were checked by a procedure outlined by Barry et al [7]. A platinum loop calibrated to deliver 0.001 ml was used. The loop was immersed vertically below the surface of the well-mixed urine specimens, and one loopful delivered to a plate of blood agar and another loopful to a CLED (cysteine lactose electrolytes-deficient) agar plate. After streaking, the plates were incubated overnight at 37°C and examined after 18 to 24 hours. A cut-off point of 100,000 CFU/ml was used for this study. The colonies were counted, and if more than 100 colonies were present, the urine sample was considered to have greater than 10^5 CFU/ml, indicating significant bacteriuria [8]. Lower counts in catheter specimens were accepted as sig-

nificant if the organisms persisted or were isolated from successive specimens. Standard diagnostic microbiological methods for identification of the isolates were used [9]. Gram-negative bacilli were identified using API 20E (La Balme Les Grottes, Vencieu, France). Antibiotic susceptibility tests were performed on significant isolates using Stokes and Waterworths method [10]. The antibiotic discs used were ampicillin, 25 mcg per disc; cotrimoxazole, 25 mcg; nitrofurantoin, 200 mcg; nalidixic acid, 30 mcg; mecillinam, 25 mcg; norfloxacin, 10 mcg; amoxicillin-clavulanic acid (Augmentin), 30 mcg; ceftriaxone, 30 mcg; gentamicin, 10 mcg; piperacillin, 100 mcg; cefuroxime, 30 mcg; and ceftazidime, 30 mcg. Staphylococci were also tested for with cloxacillin, 5 mcg per disc.

Hospital-acquired infections were defined as those that arose at three days or later following admission, or were clearly related to a procedure performed after hospitalization.

Results

During the 18-month period of study, a total of 13,193 urine specimens were collected, 8943 (68%) were from outpatient clinics and 4250 (32%) were from inpatients from different services. Significant bacteriuria was detected in 1004 specimens (7.6%); 664 (66%) were from outpatients and 340 (34%) were from inpatients.

Table 1 shows the number of patients with significant bacteriuria categorized by age group and

TABLE 1. The number of patients with significant bacteriuria in MSU and CSU by age group and sex.

Age (yr)	Total number in each age group		Male		Female	
	MSU	CSU	MSU No.(%)	CSU No.(%)	MSU No.(%)	CSU No.(%)
< 1 year	18	—	12 (1.45)	—	6 (0.73)	—
1-9	100	12	29 (3.5)	9 (5.0)	71 (8.61)	3 (1.68)
10-19	122	14	18 (2.18)	10 (5.59)	104 (12.61)	4 (2.23)
20-29	230	13	30 (3.63)	6 (3.35)	200 (24.24)	7 (3.91)
30-39	145	12	34 (4.12)	8 (4.47)	111 (13.45)	4 (2.23)
40-49	66	18	16 (1.93)	11 (6.15)	50 (6.1)	7 (3.90)
50-59	98	44	67 (8.12)	34 (18.99)	31 (3.76)	10 (5.59)
> 60	46	66	30 (3.63)	41 (22.91)	16 (1.94)	25 (13.97)
Total	825	179	236(28.6)	119(66.5)	589(71.4)	60(33.51)

MSU = midstream urine; CSU = catheter stream urine.

NB. Total No. of patients catheterized was 920; 620 were male and 300 were female. There was significant bacteriuria in 179.

sex. Significant bacteriuria was more common in females than in males at all ages, except for those under 1 year and over 50 years. Urinary tract infection was more common in the 20 to 29 year age group, and half (50.3%) of the patients with significant bacteriuria were females between 10 and 40 years old. Microscopically, all specimens from patients with significant bacteriuria showed more than three pus cells per field under a $\times 40$ objective and $\times 10$ eyepiece.

In the catheterized group, 179 of the 920 patients showed significant bacteriuria for a rate of 19.4%. The rate of bacteriuria was similar for both sexes—19.1% in males (119/620) and 20% in females (60/300). Bacteriuria was more common (61%) in patients aged 50 years and older.

Microscopically, not all patients with bacteriuria showed pyuria. The types of organisms isolated from urine specimens, and separated according to community-acquired and hospital-

TABLE 2. Types of microorganisms isolated from urine.

Organisms	Community-acquired (N = 695)	Hospital-acquired (N = 309)	Total (N = 1004)
	No. (%)	No. (%)	No. (%)
<i>Escherichia coli</i>	403 (58.0)	118 (38.0)	521 (52.0)
<i>Klebsiella-Enterobacter</i> sp.	125 (18.0)	74 (24.0)	119 (11.8)
<i>Proteus mirabilis</i>	49 (7.0)	7 (2.2)	56 (5.5)
<i>Pseudomonas</i> sp.	27 (3.8)	42 (13.5)	69 (6.8)
<i>Streptococcus</i> sp.	35 (5.0)	6 (1.9)	41 (4.1)
<i>Staphylococcus aureus</i>	18 (2.6)	21 (6.7)	39 (3.8)
<i>Citrobacter</i> sp.	8 (1.1)	9 (3.0)	17 (1.7)
<i>Serratia</i> sp.	—	19 (6.1)	19 (1.9)
<i>Morganella morganii</i>	14 (2.0)	4 (1.2)	18 (1.8)
<i>Providencia</i>	10 (1.4)	5 (1.6)	15 (1.5)
<i>Staphylococcus saprophyticus</i>	3 (0.4)	—	3 (0.3)
<i>Salmonella</i> sp.	3 ^a (0.4)	—	3 (0.3)
<i>Candida</i> sp.	—	4 (1.2)	4 (0.4)

^a The three isolates of *Salmonella* sp. were from sickle cell disease patients.

TABLE 3. Susceptibilities of gram-negative organisms isolated from urine.

Agent	Microorganism (Percentage of susceptible strains)											
	<i>Escherichia coli</i>		<i>Klebsiella-Enterobacter</i> sp.		<i>Pseudomonas</i> sp.		<i>Proteus</i> sp.		<i>Serratia</i>		<i>Citrobacter</i>	
	CA (N=304)	HA (N=118)	CA (N=125)	HA (N=74)	CA (N=27)	HA (N=149)	CA (N=49)	HA (N=7)	CA (N=19)	HA (N=8)	CA (N=8)	HA (N=9)
Augmentin	88	69	78	72	—	—	87	71	—	44	36	42
Nitrofurantoin	94	89	29	36	—	—	0	0	—	44	36	62
Nalidixic acid	88	83	89	91	—	—	82	69	—	100	68	82
Cotrimoxazole	69	58	82	80	—	—	68	58	—	72	33	32
Ampicillin	32	23	0.2	0	—	—	67	52	—	0	0	0
Mecillinam	79	84	79	72	—	—	57	57	—	0	33	32
Norfloxacin	97	94	86	88	84	81	69	82	—	49	68	82
Gentamicin	95	93	89	92	75	72	89	86	—	29	68	82
Ceftriaxone	95	90	90	92	81	80	89	86	—	58	68	82
Piperacillin	42	33	70	41	82	80	57	33	—	0	33	58
Cefuroxime	94	72	85	80	—	—	88	83	—	0	68	70
Ceftazidime	—	—	—	—	95	88	—	—	—	—	—	—

CA = community-acquired; HA = hospital-acquired.

TABLE 4. Susceptibilities of gram-positive organisms isolated from urine.

Agents	Microorganisms (percentage of susceptible strains)					
	Streptococci ^a		<i>Staphylococcus aureus</i>		<i>Staph. saprophyticus</i>	
	CA (N = 35)	HA (N = 6)	CA (N = 18)	HA (N = 21)	CA (N = 3)	HA
Ampicillin	100	100	0	0	69	—
Erythromycin	81	83	49	42	69	—
Cotrimoxazole	33	21	59	61	100	—
Augmentin	100	100	76	70	69	—
Norfloxacin	0	0	72	79	69	—
Ceftriaxone	—	—	—	—	—	—
Cloxacillin	—	—	88	72	100	—

^a Includes 32 *Streptococcus faecalis* and 9 group B. beta hemolytic streptococci.

CA = community-acquired; HA = hospital-acquired.

acquired infections, are shown in Table 2. The most frequently isolated organisms were *Escherichia coli*, *Klebsiella-Enterobacter* sp., *Pseudomonas* sp., fecal-type streptococci, *Proteus mirabilis*, and *Staphylococcus aureus*.

E. coli was the most common isolate in both inpatient and outpatient specimens. The antimicrobial susceptibilities of gram-negative organisms isolated from urine are shown in Table 3 and those for gram-positive isolates are shown in Table 4. *E. coli* showed a high resistance to ampicillin, cotrimoxazole, and piperacillin, while the same strain showed sensitivity to norfloxacin, amoxicillin-clavulanic acid (Augmentin), and ceftriaxone. *Proteus mirabilis* showed a high resistance pattern to nitrofurantoin, ampicillin, and cotrimoxazole; 25% of the *Pseudomonas* species showed resistance to gentamicin. *Serratia* sp. were highly resistant to more than one antimicrobial agent. All isolates in our series were resistant to cefuroxime, piperacillin, and ampicillin, while all isolates were sensitive to nalidixic acid.

Discussion

This study revealed there is a female preponderance of urinary tract infection at Qatif Central Hospital and our findings agree with those reported elsewhere [11,12]. The prevalence rate in the outpatient group was 7.4% (664/8943) and in the inpatient group was 8% (340/4250), which is comparable to the 7.5% reported from another part of the Kingdom [13].

Of the 920 catheterized patients (620 males and 300 females), significant bacteriuria developed in

179, yielding a catheter-related bacteriuria frequency of 19% (179/920). One hundred nineteen were males (66%) and 60 were females (33.5%), giving a male to female ratio of 1.9:1. Sixty-three percent of the male group was above the age of 50 years, and this age bias is probably due to the high incidence of prostatic hypertrophy in this group [14], which results in frequent catheterization. In the female group, age was also a risk factor and may be due to an increased incidence of pelvic surgery in the 50+ age group. However, the role of the catheter as a foreign body in urinary tract infection has been reported by others [3,15]. Bacteriuria in catheterization patients indicates that the urinary tract has become colonized or infected. Colonization may be distinguished from infection by the lack of pus cells in the urine and the absence of clinical symptoms. We consider differentiation between the two conditions mandatory, because patients with indwelling urinary catheters often have repeated episodes of bacteriuria, and this may result in the repeated administration of antimicrobial agents and the emergence of highly resistant bacteria. In our series, of 179 catheterized patients who exhibited significant bacteriuria, 103 (57.5%) proved to be cases of colonization while 76 (42.5%) were genuine infections. The spectrum of microorganisms isolated from urine was similar to that described by others [13–16].

E. coli, *Klebsiella-enterobacter* sp., *Pseudomonas* sp., *Proteus mirabilis*, and *Streptococcus faecalis* were the organisms commonly encountered. *E. coli* was the most common organism isolated in both the inpatient and outpatient groups, and rep-

resented 58% of the cases of community-acquired urinary tract infection. The overall incidence of *E. coli* in cases of significant bacteriuria in our series was 52% (521/1004).

Klebsiella-enterobacter, *Serratia* sp. and *Pseudomonas* sp. were more common in cases of hospital-acquired bacteriuria than in community-acquired bacteriuria. Analysis of antimicrobial resistance patterns revealed a very high resistance to ampicillin; 68% of the cases of *E. coli* isolated showed resistance to ampicillin for the community-acquired isolates and 77% for the hospital-acquired isolates, which is comparable to that reported for another part of the Kingdom [13]. This high frequency of resistance was expected, as ampicillin and its derivatives continue to be the most widely used antibacterial drugs used throughout the world, and our region and hospital are no different. In the developed world, there have been a few surveys indicating the true incidence of ampicillin resistance among gram-negative bacilli responsible for bacteriuria. In the United Kingdom, resistance was 21.6% in 1980 [17]. In India in 1984, 82% of the Enterobacteriaceae cases were resistant to ampicillin [18]. At our hospital, the high level of sensitivity to Augmentin implies that the resistance to ampicillin is due to beta lactamase production, the main mechanism for bacterial resistance to beta-lactam antibiotics [19,20]. *Pseudomonas* sp. showed a 95% sensitivity to ceftazidime for the community-acquired strains and 88% for the hospital-acquired strains. Cotrimoxazole is not widely used in this area due to the high prevalence of glucose-6 phosphate dehydrogenase deficiency among the residents of the Eastern Province of Saudi Arabia [21]. However, we observed a high resistance rate of urinary isolates to cotrimoxazole, which needs explanation. Resistance of *E. coli* to nitrofurantoin in our study was 6% for community-acquired strains and 11% for hospital-acquired isolates which differs from the 32% reported from King Abdulaziz University Hospital in Jeddah [13]. This difference is probably due to less frequent use of nitrofurantoin in our hospital, because of the high prevalence of G6PD deficiency in the people living in the Eastern Province.

Because of the high level of resistance to ampicillin, this drug should not be the first drug of choice for the empirical treatment of urinary tract

infection. Prior to the availability of sensitivity results in patients, we recommend the use of Augmentin or norfloxacin. Norfloxacin is particularly useful in suspected cases of *Pseudomonas* urinary tract infection.

A high count of organisms in the urine of catheterized patients is not automatically indicative of significant infection. Undoubtedly such patients have bacteriuria, but antibiotic treatment will not necessarily eradicate it and probably will select resistant strains. Our policy is to perform sensitivity tests and to use antibiotic therapy when clinically apparent episodes of infection develop, as when, for example, fever occurs for which no cause can be found.

To reduce the rate of infection or colonization in catheterized patients, we suggest that the recommendations of Macfarlane [22] be followed, consisting of: indwelling urinary catheters should be inserted only when absolutely necessary and removed as soon as possible, a pre-assembled closed sterile urinary drainage system should be used and insertion of a catheter should be performed by properly trained staff using an aseptic technique and without disconnecting the drainage tube on the collecting bag from the pre-assembled unit.

References

1. Platt R. Diagnosis and empiric therapy of urinary tract infection in the seriously ill patient. *Rev Infect Dis* 1983;5(suppl 1):S65-73.
2. Center for Disease Control. National nosocomial infections study, quarterly report. 1971;third quarter:5-8.
3. Feingold DS. Hospital-acquired infections. *N Engl J Med* 1970;283:1384-91.
4. Mycrovitz RL, Meduros AA, O'Brien TF. Recent experience with bacilemia due to negative organisms. *J Infect Dis* 1971;124:239-43.
5. Dupont HL, Spink WW. Infection due to gram-negative organisms: an analysis of 860 patients with bacteremia at the University of Minnesota Medical Center 1958-1966. *Medicine* 1969;48:307-15.
6. Hoepfich PD. Culture of urine. *J Lab Clin Med* 1960;56:899-907.
7. Barry AL, Smith PB, Turck M. Laboratory diagnosis of urinary infections, Cumitech 2, Washington D.C., American Society for Microbiology; 1975.
8. Kass EH, Miall WE, Stuart KL, Rosner B. Epidemiologic aspects of infections of the urinary tract. In: Kass EH, Brumfitt W, eds. *Infections of the urinary tract*. Chicago: University of Chicago Press, 1978;1-7.
9. Cowan ST, Steel KJ. *Manual for the identification of medical bacteria*. Cambridge: Cambridge University Press, 1970;77-122.
10. Stokes EJ, Waterworth PM. Antibiotic sensitivity test by diffusion method. *Assoc Clin Pathol Board* 1972;55:1-12.

11. Jepsen OB, Larsen SO, Dankert K, et al. Urinary tract infection and bacteraemia in hospitalized medical patients—a European multicentre prevalence survey on nosocomial infection. *J Hosp Infect* 1982;3:241-52.
12. Meers PD, Ayliff GAJ, Emmerson, et al. Survey of infection in hospitals 1980. *J Hosp Infect* 1981;2(suppl, Dec):23-8.
13. El-Tahawy AT, Khalaf RMF. Urinary tract infection at University Hospital in Saudi Arabia: incidence, microbiology, and antimicrobial susceptibility. *Ann Saudi Med* 1988;8(4):261-6.
14. Rickards D. Imaging the prostate. *Clin Radiol* 1989;40:335-6.
15. Stamm WE. Guidelines for prevention of catheter associated urinary tract infections. *Ann Intern Med* 1975;386-90.
16. Bernander S, Hanbroeus A, Myrback KE, et al. Prevalence of hospital-associated infections in five Swedish hospitals in November 1975. *Scan J Infect Dis* 1970;10(1):66-70.
17. Simpson IN, Harper PB, O'Callaghan CH. Principal B. lactamases responsible for resistance to B. lactam antibiotics in urinary tract infections. *Antimicrobial Agents Chemother* 1980;17:929-36.
18. Nandivada LS, Amyes SGB. Transferable resistance to Beta-lactam antibiotics in gram-negative bacteria in India. *Pharm Pharmacol*, 1987;39:18.
19. Anderson ES, Datta N. Resistance to penicillin and its transfer to Enterobacteriaceae. *Lancet* 1965;1:407-9.
20. Amyes SGB. Plasmid mediated B-lactamases—relative clinical importance. In: Livermore DM, ed. *Beta-lactamases—current perspectives*. Winchester: Theracom, 1988;31-50.
21. El-Hazmi MAF. Haemoglobin disorder: a pattern for thalassemia and haemoglobinopathies in Arabia. *Acta Haematol (Basel)* 1982;68(1):43-51.
22. Macfarlane DE. Prevention and treatment of catheter associated urinary tract infection. *J Infect* 1985;10:96-106.

HELICOBACTER PYLORI AND CHRONIC GASTRITIS

Khalid Mahmood, MD, FRCPath(London)

استقصينا التهاب المعدة المزمن بالفحص النسيجي وكذلك وجود العصيات اللولبية البوابية لدى ١٤٨ مريضاً عربياً من كلا الجنسين يعانون من أعراض عسر الهضم. تؤكد هذه الدراسة مجدداً وجود الترابط بين الحالتين وتقرح صلة سببية بينهما. إن تطفل العصيات اللولبية البوابية بقرب التهاب المعدة الضموري يؤكد أهمية المتابعة المديدة لهذه الحالات للتحقق من أية صلة لها بحدوث سرطان المعدة.

One hundred forty-eight Arab patients of both sexes who had dyspeptic symptoms were histologically examined for the existence of chronic gastritis and the presence of *Helicobacter pylori*. This study further confirms this association and suggests an etiological link between these two conditions. The infestation of *Helicobacter pylori* adjacent to atrophic gastritis warrants prolonged follow-up of affected cases to prove any relationship to the development of gastric cancer.

Since the beginning of this century histopathologists have been aware of the presence of spiral organisms in the stomach of man. In 1983, Warren [1] and Marshall [2] noticed the presence of curved bacilli in gastric biopsy specimens obtained from patients with active chronic gastritis. Subsequently, these organisms were grown from antral biopsy material [3]. This came about by chance when the culture plates were left to incubate for longer than the usual period over an extended Easter holiday. To date various centers worldwide have done studies and found a strong association between chronic gastritis and the presence of these organisms in the stomach.

The present histological study was carried out in the Arab population of the Kingdom of Saudi Arabia to explore the possibility of a link between *Helicobacter pylori* (HLO) and gastritis. To the best of my knowledge, there is no documentation of this link in Saudi literature.

Material and Methods

Mucosal biopsy specimens from the gastric antrum obtained about 2 to 4 cm from the pylorus, duodenal bulb and esophagus were procured from 148 patients with nonulcer-related dyspepsia. In addition, six patients with gastric carcinoma were also studied. The biopsy site and age and sex of the patients are given in Table 1. Two biopsy specimens were taken from the antrum, duodenum, and esophagus.

The specimens were fixed in 10% formalin and routinely processed. Three-micrometer-thick sections were stained with hematoxylin-eosin and the Warthin Starry technique for identification of mucosal *Campylobacter pylori*. Periodic acid-Schiff was used for identification of metaplasia.

TABLE 1. Age, sex, and biopsy site.

Patient age range	14-90+ yr
Sex	93, male 55, female
Biopsy sites	
Antral biopsies including 6 cases of gastric carcinoma	126 cases
Duodenal biopsies	27 cases
Esophageal biopsy	1 case

From the Department of Pathology, College of Medicine, King Saud University, Riyadh.

Address reprint requests and correspondence to Dr. Mahmood: Department of Pathology (32), College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Accepted for publication 27 August 1990.

The presence and degree of inflammation in the stomach were graded according to Whitehead's [4] classification.

The duodenal histology was graded as follows: *Normal*: a normal duodenal architecture with vilus crypt ratio of 2:1 in most areas with or without Brunner's glands in the lamina propria, with no increase in cellularity or evidence of epithelial change. *Mild duodenitis*: a definite increase in the mononuclear cells in the lamina propria without any evidence of epithelial damage. *Chronic duodenitis*: a definite increase in the mononuclear cells in the lamina propria with evidence of epithelial damage.

Results

Of antral biopsy specimens obtained in 120 cases, three showed no chronic gastritis, while the remaining 117 cases showed chronic gastritis and active chronic gastritis. One hundred thirteen cases showed colonization of the gastric mucosa with HLO (*Helicobacter*-like organisms). Three cases showed atrophic gastritis, and one of these also showed intestinal metaplasia. Thus, 96.5% of these cases showed colonization by HLO. In one case, a columnar surface epithelium esophageal biopsy specimen showed chronic inflammation and some colonization with HLO above the surface epithelium. Of the 27 cases with duodenal biopsy specimens, 18 showed mild duodenitis and one case showed gastric heterotopia. All these cases showed no colonization with HLO. Nine showed active duodenitis with a greater than 5% area of gastric metaplasia of the surface epithelium; two cases also showed duodenal ulceration. All these showed colonization by HLO. An additional six cases of gastric carcinoma also showed changes associated with chronic active gastritis with colonization of HLO in the adjacent mucosa.

Discussion

The association between the presence of HLO in the gastric mucosa and histologically confirmed gastritis in patients with dyspeptic symptoms is well recognized by different workers [5,6]. These spiral organisms in gastric biopsy material are recognized by routine hematoxylin-eosin staining, but with the application of special stains, such as

Giemsa, cresyl violet, acridine orange, modified Gram's stain, and Warthin Starry stain, they are visualized easily. I found these organisms easily in antral biopsy material stained with hematoxylin-eosin. I also used Warthin Starry stain to spot these organisms. These organisms were seen in the mucous layer covering the surface epithelium (Figure 1) and in the surface crypt. Of 148 cases examined, 117 had antral biopsy specimens that showed chronic gastritis. Of these, 113 specimens showed colonization by HLO. The number of the organisms was greater in those biopsies showing activity, that is, showing acute polymorphonuclear infiltration of the lamina propria (Figure 2) and the surface or crypt epithelium. This finding has been confirmed by other workers [7-11]. In this study the patient's age ranged from 20 to 90 years, and it was noticed that, although in some biopsies the magnitude of the chronic active gastritis was greater among the younger patients,

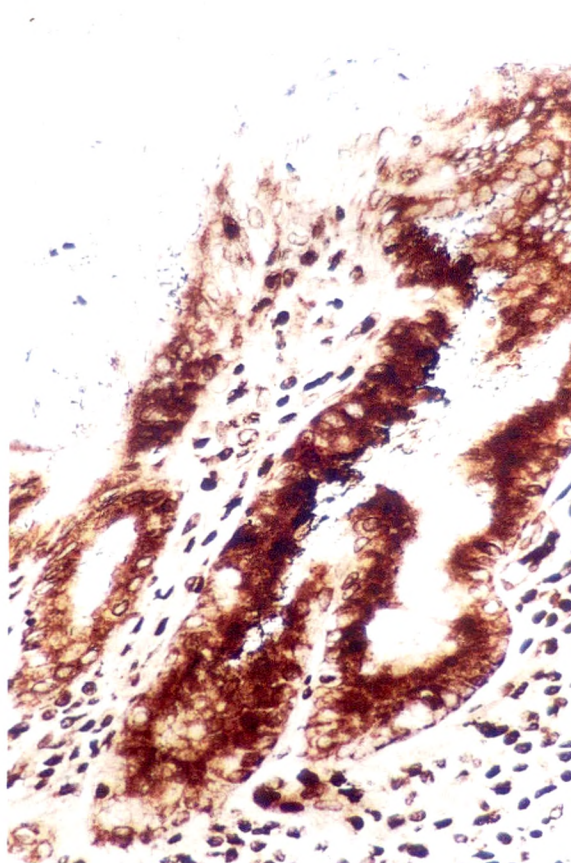


FIGURE 1. *Helicobacter pylori* in the surface mucous layer. (Warthin Starry stain; original magnification, $\times 400$.)

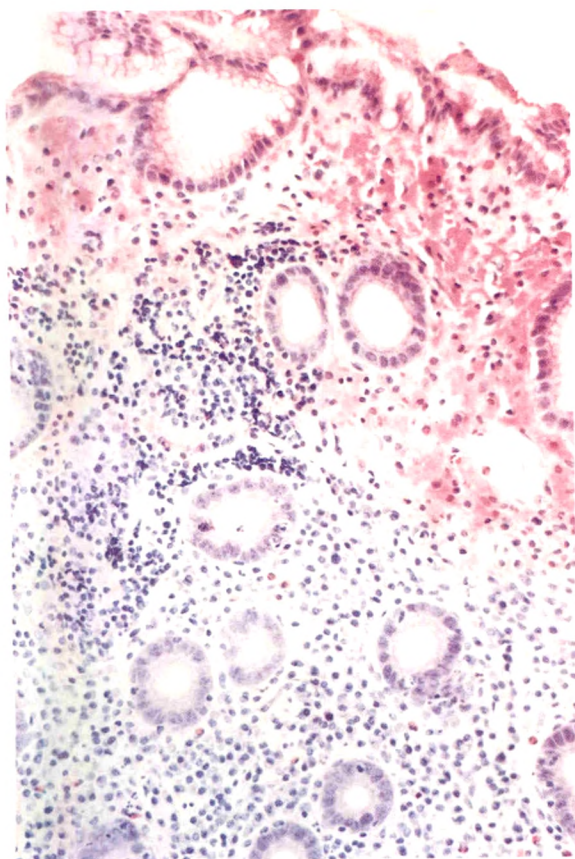


FIGURE 2. Pyloric antral mucosa showing active chronic inflammation. (Hematoxylin-eosin; original magnification $\times 250$.)

there was no corresponding increase in the number of organisms. However, the magnitude of colonized organisms was increased with age and with the activity of gastritis from age 40 and older. This age-related increase of prevalence in gastritis with HLO colonization has been documented by Marshall and Warren [12].

Spiral bacteria are not normally seen in the duodenum. In this study, of 27 cases with duodenal biopsy specimens, 18 showed mild duodenitis; one also showed gastric heterotopia. Nine cases showed active duodenitis, with areas of gastric metaplasia exceeding 5% and two cases showing ulceration. All the cases showing active duodenitis showed some colonization by HLO. It is believed that gastric metaplasia in the proximal duodenum is related to high gastric acidity. The ulceration of duodenal mucosa follows colonization of the area affected by gastric metaplasia. Marshall et al [3] suggested that colonization of these areas of intestinal metaplasia by HLO

causes duodenal ulceration. Wyatt et al [13] also suggested that acid induces gastric metaplasia in the duodenum and HLO associated gastritis may be synergistic in the pathogenesis of duodenitis. The metaplastic gastric epithelium allows HLO to colonize the duodenal mucosa where it produces an acute inflammatory response.

Once again, spiral organisms are not normally seen in esophageal squamous epithelium. I have examined nearly 100 esophageal biopsy specimens for other purposes, and in doing so have never found colonization of the esophageal epithelium by HLO. One patient in this study, with dyspeptic symptoms, exhibited a Barrett's type esophageal mucosa showing inflammation with some colonization by HLO. Paull et al [14] found these organisms in the columnar lined epithelium in four of 26 patients with Barrett's esophagus. Hazell et al [15], in a study of 20 cases of Barrett's esophagus with gastric type epithelium, found eight had ulcers and three of these showed spiral organisms in active chronically inflamed gastric-type epithelium.

Eighty-six of these antral biopsy specimens were also cultured on Skirrows selective media, although I was not aware of the results at the time of histological examination and was told that 77% grew HLO. All of these patients, except two, also had a rapid urease test [16], which was positive in 61.

This study again highlights the strong association of chronic gastritis in 96.5% of the cases with colonization by HLO in the stomach. This association in patients with non-ulcer-related dyspepsia suggests an etiological link, because the presence of bacteria excites an inflammatory response and the presence of organisms attracts polymorphonuclear cells in the mucous layer. Body-type mucosa also showed bacteria and inflammation. Similarly, duodenum showed HLO only in cases of active duodenitis in the area of gastric metaplasia. Ultrastructural studies conducted by Chen et al [17] on HLO-associated gastritis have provided evidence in support of a pathogenetic and etiological role of HLO, in that the organism and the underlying mucosal cells have been seen to be attached by what is termed an *adherence pedestal*. Additionally, the underlying epithelial mucous-secreting cells may show evidence of structural damage. These morphological features disappear after the eradication of HLO. This further con-

firms the causal relationship between chronic gastritis and HLO. We have not yet done any studies after treatment.

In three cases the presence of atrophic gastritis adjacent to the area showing colonization of the mucosa by these bacteria warrants follow-up of these cases to prove the hypothesis which suggests a chain of events in the development of gastric carcinogenesis by *C. pylori* as an environmental factor. The significance of infestation by HLO adjacent to a cancerous stomach is difficult to interpret as a causative factor in the pathogenesis of gastric carcinogenesis when there is no repeat follow-up of the precancerous lesions subsequent to HLO challenge. This warrants further study.

Acknowledgment

I am thankful to Drs. R. S. Rasheed, I. A. Mofleh, Prof. E. A. Ayoola of the Gastroenterology Division, and Prof. M. N. H. Chowdhury of the Microbiology Department, King Khalid University Hospital, for providing material for histopathological study and for microbiology results in these cases. I am also thankful to Mr. Salahuddin Khan for typing this manuscript.

References

- Warren JR. Unidentified curved bacilli of gastric epithelium in chronic active gastritis. *Lancet* 1982;1:1273.
- Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983;1:1273-5.
- Marshall BJ, Royce H, Annear DI. Original isolation of *Campylobacter pyloridis* from human gastric mucosa. *Microbios Lett* 1985;25:83-8.
- Whitehead R. Mucosal biopsy of the gastro-intestinal tract, ed 3. Philadelphia: Saunders, 1984.
- Goodwin CS, Armstrong JA, Marshall BJ. *Campylobacter pyloridis*, gastritis, and peptic ulceration. *J Clin Pathol* 1986;39:353-65.
- Vaira D, Holton J, Osborn J, et al. Use of endoscopy in patients with dyspepsia. *Br Med J* 1989;299:237.
- McNulty CAM, Watson DM. Spiral bacteria of the gastric antrum. *Lancet* 1984;1068-9.
- Phillips AD, Hine KR, Holmes GKT, Woodings DF. Gastric spiral bacteria. *Lancet* 1984;2:100-1.
- Steer WH. The gastroduodenal epithelium in peptic ulceration. *J Pathol* 1985;146:355-62.
- Johnson BJ, Reed PI, Ali MH. *Campylobacter*-like organisms in duodenal and antral endoscopic biopsies: relationship to inflammation. *Gut* 1986;27:1132-7.
- Hazell BL, Hennessy W, Borody TJ, et al. *Campylobacter pyloridis* gastritis: II, distribution of bacteria and associated inflammation in the gastroduodenal environment. *Am J Gastroenterology*, 1987;82:297-301.
- Marshall BJ, Warren JR. Unidentified curve bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984;1:1311-5.
- Wyatt JJ, Rathbone BJ, Dixon MF, Heatley RJ. *Campylobacter pyloridis* and acid induced gastric metaplasia in the pathogenesis of duodenitis. *J Clin Pathol* 1987;40:841-8.
- Paull G, Yardley JH. Gastric and esophageal *Campylobacter pylori* in patients with Barrett's esophagus. *Gastroenterology* 1988;95:216-8.
- Hazell SL, Carrick J, Lee A. *Campylobacter pylori* can infect the esophagus when gastric tissue is present (abstract). *Gastroenterology* 1988;94:178.
- Arvind AS, Cook RS, Tabaqchali S, Farthing MJGF. One minute endoscopy room test for *Campylobacter pylori* (letter). *Lancet* 1988;704.
- Chen XG, Correa P, Offerhaus J, et al. Ultrastructure of the gastric mucosa harbouring *Campylobacter*-like organisms. *Am J Clin Pathol* 1986;86:575-82.

INCREASING COMPLIANCE OVER FIVE YEARS IN A HEPATITIS B INFANT IMMUNIZATION PROGRAM IN SAUDI ARABIA

Frank W. Kiel, M.D.

بدأ في شهر يوليو ١٩٨٤م برنامج لتمنيع الأطفال الذين ولدوا وأمهاتهم تحمل حمة التهاب الكبد من نوع ب وذلك في مستشفى الملك فهد للحرس الوطني. وبعد مرور ثلاثة عشر شهراً على البرنامج تبين وجود إيجابية التفاعل للمستضد السطحي لالتهاب الكبد ب لدى ما نسبته ٣,٨٪ من الأمهات، وكان أقل من نصف الحوامل قد راجعن لتلقي الرعاية أثناء الحمل، وأتم سلسلة التلقيح ما نسبته ٢٨٪ فقط من الأطفال المعرضين. وخلال فترة السنوات الخمس الأولى من البرنامج (١٩٨٤ - ٨٨). كان هناك ١٣٠٠٠ وليداً منهم ٤٩٠ مولوداً تحمل أمهاتهم حمة التهاب الكبد. ارتفعت نسبة النساء اللائي راجعن عيادة الحوامل مرة واحدة على الأقل من نسبة ٤٦٪ في عام ١٩٨٤م إلى نسبة ٦٦٪ في عام ١٩٨٧م. وتبين بتحليل النتائج أن نسبة المراجعة لتلقي الجرعة الثانية من اللقاح قد ارتفعت من ٤٩٪ عام ١٩٨٤م إلى ٧٤٪ في عام ١٩٨٨م، وللجرعة الثالثة من اللقاح من ٢١٪ في عام ١٩٨٤م إلى ٥١٪ في عام ١٩٨٨م. أجريت الاستقصاءات لتحديد حالة المناعة بعد استكمال سلسلة التلقيح. ومن ١٢٧ طفلاً تم فحصهم، كان ١٢٦ منهم سلبين للمستضد السطحي لالتهاب الكبد ب وأظهر واحد فقط إيجابية هامشية. ومن ١٢٥ طفلاً تم فحصهم لعد التهاب الكبد ب، تحقق التحول المصلي لدى ٨٧٪.

Immunization of babies born to hepatitis B carrier mothers at King Fahad National Guard Hospital began in July 1984. Thirteen months into the program, it was learned that 3.8% of the mothers were HBsAg positive, that less than half of the pregnant women came for any prenatal care, and that only 28% of the infants at risk completed the vaccination series. During the first five years (1984-88) of the program, there were 13,000 newborns, of whom 490 were born to hepatitis carrier mothers. The percentage of women who came for at least one prenatal visit increased from 46% in 1984 to 66% in 1987. Analysis showed that the percentage of return for the second vaccination increased from 49% in 1984 to 74% in 1988, and for the third vaccination from 21% in 1984 to 51% in 1988. Screening tests to determine immunity status were conducted after completion of the vaccination series. Of 127 infants tested, 126 were HBsAg negative and one was borderline positive. Of 125 infants tested for anti-HBs, 87% showed seroconversion.

In July 1984, King Fahad National Guard Hospital, Riyadh, began to prophylactically immunize the infants born to mothers who were hepatitis B carriers. In a preliminary report on the program, it was determined that 3.8% of pregnant women were HBsAg-positive; of this group 7% were HBeAg-positive [1].

In a preliminary report concerning the first thirteen months of the program, it was reported that 99% of the babies received the first vaccination; of that group, 51% received the second vaccination; of those who received the second vaccination, 57% received the third injection to complete the series. Thus, only 28% of the targeted infants had the complete hepatitis vaccination series [1]. Concerned observers questioned whether this degree of compliance was enough to meet the goal of the program and to justify its continuation [2].

This current study was undertaken to determine whether, after five years, the various attempts to

From the Department of Pathology, King Fahad National Guard Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Kiel: Route 2, Box 221C, Comfort, Texas 78013, U.S.A.

Accepted for publication 9 September 1990.

improve the program had increased the level of compliance.

Methods

Each pregnant woman was screened for hepatitis carrier status on her first hospital encounter, whether prenatal or at delivery. Most of the patients were Saudis, living in rural areas. An occasional expatriate wife received care at the hospital, but as a group they represented less than 1% of the deliveries. Screening was repeated with each subsequent pregnancy to determine if there had been a change. Not all pregnancies were carried to term, and women with spontaneous abortion or hydatidiform mole were included.

Blood testing was done using the enzyme-linked immunoassay technique (Auszyme II by Abbott for HBsAg, EIA Diagnostic Kit by Abbott for HBeAg, AUSAB EIA by Abbott for anti-HBs, Corzyme by Abbott for anti-HBc). On HBsAg-positive specimens, serum was retained and tested for HBeAg. Children who completed the vaccination series were tested for HBsAg, anti-HBs, and anti-HBc.

Infants born of HBsAg-positive mothers were immunized at birth, one month of age, and six months of age. Initial immunization was with 0.5 ml (100 IU) hepatitis B immune globulin (HBIG) (Hepumann Berna, Swiss Serum and Vaccine Institute, Berne) administered intramuscularly into the shoulder. The hepatitis vaccine was given intramuscularly into the thigh; for three years 0.5 ml (10 µg) of human-derived vaccine (H-B Vax, Merck Sharp and Dohme, West Point, Pennsylvania, USA) was used. Recombinant vaccine was introduced in 1987 using varying manufacturer-prescribed dosages before settling on 5 µg (H-B Vax II, Merck Sharp and Dohme, Haarlem, Netherlands; Recombivax Merck Sharp and Dohme, West Point, Pennsylvania, USA; Engirix-B, Smith Kline and French, Rixensart, Belgium).

Results

Source of First HBsAg Testing

For optimal effect, HBIG should be given soon after birth. To accomplish this, the mother's status should be determined prenatally. HBsAg testing

was done daily at this hospital to permit determination of the status before discharge from the hospital even in those who had no prenatal care and arrived only for delivery.

In 1984, less than half of the women came for prenatal care. By 1987, 66% had received prenatal care, including determination of HBsAg status (Table 1). The babies of the prenatally examined patients generally received the immune globulin injection and the vaccination within the first hour after delivery. For other babies, whose mothers' carrier status could not be determined until the time of delivery, the required immunizations were generally completed within 24 hours of birth.

Infant Vaccination Series

The first vaccination was given to 99% of the newborns, generally on the day of birth. In the 490 babies with hepatitis carrier mothers identified in the five years studied, only four were not vaccinated. Two were missed. The third, a 600-gm premature infant, died at 8 hours. The fourth had severe hydrocephalus and was not vaccinated (Table 2).

TABLE 1. Timing of first testing at which hepatitis B carrier status was identified.

Year	Delivery	Prenatal
	No. (%)	No. (%)
1984	33 (56)	26 (44)
1985	64 (61)	41 (39)
1986	59 (47)	67 (53)
1987	38 (34)	75 (66)
1988	68 (46)	79 (54)

TABLE 2. Vaccination series follow-up in infants at risk because they were born of hepatitis B mothers.

Year	New-borns	At risk	1st vaccination	2nd vaccination	3rd vaccination
			No. (%)	No. (%)	No. (%)
1984	881	47	46 (98)	23 (49)	10 ^a (21)
1985	2174	92	91 (99)	51 (55)	31 ^a (33)
1986	2830	116	116 (100)	72 (62)	34 (29)
1987	3332	95	93 (98)	60 (63)	32 (34)
1988	3787	140	140 (100)	104 (74)	71 (51)
Total	13004	490	486 (99)	310 (63)	178 (36)

^a One child died prior to the planned third injection.

There were 16 in the premature group who weighed under 2000 gm, the lightest weighing 990 gm. Some were vaccinated at birth, with a weight as low as 1675 gm. Others were vaccinated after they had gained weight. A policy was established to withhold vaccination until a weight of 2000 gm was achieved. All, however, received HBIG at birth.

The rate of return for the second injection of the vaccination series at four weeks of age rose from 49% in 1984 to 74% in 1988. The rate of return for the third injection at six months, to complete the series, rose from 21% in 1984 to 51% in 1988 (Table 2).

Follow-up

An additional test of the vaccinated infant after completion of the series was sought, usually at three months after the third injection, when passive anti-HBs from the mother is gone, although anti-HBc may persist. Of those tested, none became definitely HBsAg-positive, although there was one borderline result. Immunization, as indicated by the presence of anti-HBs, was achieved in 87% (Table 3).

This evaluation step in the vaccination program was recommended, but not aggressively pursued, because a sampling of the vaccinated population was considered adequate. Nevertheless, in 1988 nearly twice as many returned to be tested as in 1987 (Table 3).

TABLE 3. Follow-up testing after completion of vaccination series.

Year	No. of subjects	HBsAg		Anti-HBs	
		Positive	Negative	Positive	Negative
1984	4	0	4(100%)	4(100%)	0
1985	18	0	17 ^a (100%)	14(78%)	4(22%)
1986	24	0	24(100%)	21 ^b (91%)	2(9%)
1987	28	0	28(100%)	21 ^b (81%)	5(19%)
1988	54	1 ^c (2%)	53(98%)	49(91%)	5(9%)
Total	128	1(1%)	126(99%)	109(87%)	16(13)

^a Quantity not sufficient to test HBsAg in one patient.

^b Quantity not sufficient to test anti-HBs in one patient in 1986 and two patients in 1987.

^c Borderline positive, with anti-HBs negative, anti-HBc positive, anti-HBe negative, and anti-HBcIgM negative; quantity not sufficient to test HBeAg.

Discussion

With the passage of time and the development of trust, greater compliance by the families has occurred. Initially, the poor compliance was attributed to the fact that modern medical services were a new concept for the largely rural population served and preventive medicine measures were not understood. Specific factors identified were: (1) remote locations of many families; (2) lack of telephones, making it difficult to contact families that do not keep appointments; (3) the necessity for a close male relative to accompany the patient to the clinic; and (4) mistrust of injections which appear to hurt the child when he or she is not acutely ill [1].

Changes have been made in the original program to enhance compliance, which included: (1) providing only one future appointment slip at a time, rather than the whole series, which was often confusing; (2) maintenance of a nursery log of infants needing the vaccination series, in which telephone numbers are recorded; and (3) use of specific pediatric clinics under the direction of one pediatrics consultant, to which all babies requiring hepatitis immunization or follow-up are referred, instead of dispersing them throughout multiple clinics with multiple pediatricians of varying interests.

The achievement of seroconversion in 87% of the babies completing the vaccination series is considered acceptable in view of seroconversion rates of 75 to 100% in various reported series [3].

Poor compliance with the hepatitis B vaccination program may negate the desired outcome. In Jeddah, noncompliance among high-risk health care workers improved after employee health service follow-up measures were instituted [4]. In Riyadh, a maternity hospital study conducted from 1987 to 1989 found that only 34.2% of the infants completed the vaccination series [5].

In January 1990, King Fahad National Guard Hospital instituted the universal hepatitis vaccination program, whereby all infants, regardless of the mother's carrier status, are given a series of vaccinations against hepatitis B. Previous procedures were continued, however, including the HBsAg screening of all pregnant women; babies of hepatitis carriers were given HBIG in addition to the vaccination series. This program not only

prevents possible vertical transmission, but also enhances the hospital's infection control program by identifying hepatitis carriers.

Acknowledgment

I would like to recognize the obstetricians and pediatricians who supported this program, especially Dr. Jean Paul Dery who was Chairman of the Department of Obstetrics and Gynecology, Dr. Hassan Yaish who was Chairman of the Department of Pediatrics, Dr. Gasudraz Ahmed who was Head of Neonatology Service, and Dr. Amir Kagalwalla in whose pediatric gastroenterology clinics many of the later vaccinations and post-vaccination screening tests were done. I would also like to acknowledge Zafar Hamid, Supervisor of the Chemistry Section in the Department of Pathology, under whose direction the testing was done.

References

1. Kiel FW. Hepatitis B antigenemia among pregnant Saudi women and efforts to immunize their children. *Ann Saudi Med* 1987;7:165.
2. Arya SC. Viral hepatitis in Saudi Arabia: what next during the 1990's? *Saudi Med J* 1989;10:267-72.
3. Smego RA, Halsey NA. The case for routine hepatitis B immunization in infancy for populations at increased risk. *Pediatr Infect Dis J* 1987;6:11-19.
4. Shobokshi OA. Strategy for immunization against viral hepatitis diseases. Presented at the 1st International Symposium on Recent Advances in Immunization and Immunotherapy. WHO/Int Comp Vir Org, Riyadh 1990.
5. Hassonah/MH. Antenatal hepatitis B virus screening for all patients and controversies towards mass immunization of the newly born. Presented at the Symposium on Recent Advances in Immunization & Immunotherapy. WHO/Int Comp Vir Org, Riyadh, 1990.

PULMONARY TUBERCULOSIS IN SAUDI ARABIA: A RETROSPECTIVE STUDY OF 1566 PATIENTS

Mohammed Saleh Al-Hajjaj, FRCPC; Lalit Pandya, MRCP; Ali A. Marie, MB, BS;
Abdul Aziz Madani, MB, BS; Nasser Al-Sharif, MB, BS; Sulaiman Al-Majed, FRCPC

أجريت دراسة على ١٥٦٦ مصاباً بالتدرن الرئوي تم تنويمهم في مستشفى صحارى للأمراض الصدرية بالرياض في الفترة بين شهر يوليو ١٩٨٣م وشهر أغسطس ١٩٨٧م، شملت الدراسة مراجعة السجلات الطبية والصور الاشعاعية للمصدر ونتائج فحص القشع. شكلت فئة الأعمار التي تتراوح بين ٢١ إلى ٣٠ سنة ٤٠,٧% من مجموع المرضى، مما يشير إلى الحاجة إلى إجراء تحسين في التدابير المتخذة للسيطرة على الدرر في وسط الشباب الذين قد تضعف مقاومتهم على الرغم من تطعيمهم بلقاح ب ث ج في الطفولة. كانت نسبة غير السعوديين أكثر من نصف من تم تنويمهم مما يثير استفساراً حول مدى فاعلية الإجراءات الحالية للاستقصاء عن التدرن الرئوي لدى القادمين إلى المملكة. إن نظام العلاج بالعقاقير الأربعة وهي ريفامبيسين، وأيسونيازيد، وبايرازناميد، وإيثامبيوتول شديد الفعالية في تحقيق انقلاب قشعي مبكر عندما يخضع للمراقبة الصحيحة. وبناء على نتائج هذه الدراسة فإنه تصح التوصية بتحقيق اللامركزية في خدمات الدرر وإلحاقها بالمستشفيات الأخرى المحلية والعامه.

A review was conducted of 1566 cases of pulmonary tuberculosis admitted to Sahary Chest Hospital in Riyadh between July 1983 and August 1987. The medical records, chest radiographs, and sputum results were studied. The 21 to 30 year age group represented 40.7% of all patients, which indicates the need for improving measures for the control of tuberculosis in young adults, whose protection may have waned despite BCG vaccination in infancy. Non-Saudi male patients constituted more than half of the admissions which raises the question of the efficacy of the current pulmonary tuberculosis screening policy for individuals entering the Kingdom. The four-drug regimen of rifampicin, isoniazid, pyrazinamide, and ethambutol, when properly supervised, was very effective in achieving early sputum conversion. Based on results of this study, decentralizing tuberculosis services and attaching them to other local and general hospitals appears to be recommended.

Tuberculosis is declining in incidence in industrial countries but still poses a major health problem in almost all developing countries, and Saudi Arabia is no exception. Although health services have improved enormously, tuberculosis is still in evidence and its control presents a challenge to all health care planners [1,2]. In spite of the magnitude of this problem, information on the pattern

and extent of this disease in the Saudi medical literature is scanty, and only a few reports have been published that address the problem [1-5]. Sahary Chest Hospital is one of the largest chest hospitals in Saudi Arabia and is the main referral site for the central region of the Kingdom. A retrospective study of all cases of pulmonary tuberculosis admitted to this hospital over a four-year period was carried out.

From the Sahary Chest Hospital (Drs. Pandya, Marie, Madani, Al-Sharif), and King Saud University (Drs. Al-Hajjaj, Al-Majed), College of Medicine, King Saud University, Riyadh.

Address reprint requests and correspondence to Dr. Al-Hajjaj: Department of Medicine, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Accepted for publication 5 November 1990.

Material and Methods

The medical records of patients with the diagnosis of pulmonary tuberculosis who were admitted to Sahary Chest Hospital between July 1983 and August 1987 were thoroughly reviewed.

Diagnosis of pulmonary tuberculosis was based on direct sputum examination for acid-fast bacilli and/or culture of *Mycobacterium tuberculosis*. In the event of negative bacteriological studies, patients with a typical clinical and radiological manifestation as well as positive tuberculin test and favorable response to antituberculous therapy were presumed to have the disease.

A data collection form was completed by the investigators that recorded each patient's age, sex, nationality, clinical presentation, results of sputum examination, radiological findings, and outcome of therapy. At least three sputum samples were submitted for direct smear and culture for acid-fast bacilli before starting antituberculous therapy. A standard regimen of rifampicin, isoniazid, pyrazinamide, and ethambutol or streptomycin was given for the first two months. Thereafter, only rifampicin and isoniazid were continued for an additional seven months. After 4 weeks of treatment, sputum smears were checked daily, and if three consecutive samples were negative, patients were considered to have converted and arrangements for discharge from the hospital and follow-up were made. If any one sample from a patient was still positive, then he/she was kept in the hospital and continued on drug therapy. Thereafter, and at 2-week intervals, sputum samples were collected and the same process was followed until the patient became negative. Positive sputum samples after 3 months of therapy raised the suspicion of drug resistance. However, because sensitivity tests were available only for limited samples, the same drug regimen was continued in order to maximize the conversion rate. Second-line therapy (which is described below) was then given to the remaining patients who showed no sputum conversion after six months of therapy.

Laboratory investigations for complete blood count; hemoglobin, urea, and creatinine concentration; and liver function tests were done at the time of admission and then at two-week intervals until the patient was discharged from the hospital. Patients who present for the first time and with no previous history of pulmonary tuberculosis were called new cases, while those with a past history of tuberculosis or with typical changes on the chest x-ray study, such as apical fibronodular changes, were called old cases. The pattern of the disease

on chest roentgenograms was described according to the standard classification [6]. Statistical analysis was done using the chi-square method, and $P < 0.05$ was considered significant.

Results

Demographic Data

A total of 1566 patients were admitted during a four-year period, at an average rate of 32.6 patients per month. Of these, 1195 (76.3%) were males and only 371 (23.7%) were females. The most frequent age group was 21 to 30 years (42.2% for males, 35.6% for females) (Table 1). Saudi patients constituted just less than half of the admissions; these were 747 (47.7%) with 486 males and 261 females. Non-Saudi males represented the highest category of patients (709; 45.3%) (Table 2). Non-Saudi patients tend to be younger, with a mean age of 36 and 35.2 years for males and females, respectively, compared with mean ages of 41.5 and 39.9, respectively, for Saudi patients. The distribution of patients according to nationality is shown in Table 3. Yemeni patients were by far the most common group after Saudis, constituting 19.9% of the total.

TABLE 1. Age and sex distribution of patients with pulmonary tuberculosis.

Age (yr)	Males	Females	Both sexes
	No. (%)	No. (%)	No. (%)
Under 11	2 (0.2)	5 (1.3)	7 (0.5)
11-20	88 (7.3)	72 (19.4)	160 (10.2)
21-30	505 (42.3)	132 (35.6)	637 (40.7)
31-40	267 (22.3)	60 (16.2)	327 (20.9)
41-50	114 (9.5)	47 (12.6)	161 (10.3)
51-60	98 (8.2)	23 (6.2)	121 (7.7)
61-70	56 (4.7)	15 (4.0)	71 (4.5)
above 70	65 (5.4)	17 (4.6)	82 (5.2)
Total	1195	371	1566

TABLE 2. Distribution of patients according to nationality and sex.

Nationality	Males	(%)	Females	(%)	Total
Saudi†	486	(40.7)	261	(70.4)	747
Non-Saudi	709	(59.3)	110	(29.6)	819
Total	1195		371		1566

TABLE 3. *Distribution of patients according to country of birth.*

Nationality	No.	Percentage
Saudi	747	47.7
Yemeni	312	19.9
Pakistani	88	5.6
Indian	83	5.3
Filipino	70	4.5
Egyptian	59	3.7
Somali	35	2.2
Indonesian	25	1.6
Eritrean	21	1.3
Sudani	21	1.3
Turki	18	1.2
Bangladeshi	14	1.1
Thai	11	0.7
Others	40	2.5
Total	1544	

Clinical Symptoms

There was a past history of treated or untreated pulmonary tuberculosis in 454 patients ("old" cases); 65.7% were Saudis and 36.3% were non-Saudis. The remaining 1112 patients represented new cases (i.e., those who presented for the first time). Cough with or without expectoration was the most frequent symptom at presentation (94.3%). Fever and other constitutional symptoms were seen in 77.7% of the cases. Hemoptysis was the presenting symptom in 40.7% of the cases and was more common in previously treated patients than in new patients 237/454 (52%) and 414/1112 (37%), respectively ($P < 0.001$).

Radiological Patterns

Minimal disease was seen in 19%, moderately advanced in 48.4%, and far advanced in 26.6% of the cases. Associated cavitory disease was seen in 718 patients (45.8%). Pleural effusion was present in 58 (3.7%) patients while the miliary pattern was seen in 18 patients only (1%).

Laboratory Results

Hemoglobin concentration was less than 13 g/dL in 45.7% of males and below 12 g/dL in 46.5% of females on admission. Average erythrocyte sedimentation rate (ESR) on admission was 68.3 mm/first hour for males and 75.7 mm/first hour for females. After initial therapy and upon discharge, the ESR decreased by 45.3% and 40.2% in males

and females, respectively. The average uric acid level on admission was 285.8 $\mu\text{mol/L}$ for males and 305.9 $\mu\text{mol/L}$ for females on admission. These levels almost doubled upon discharge from hospital (565 $\mu\text{mol/L}$ for males and 508.8 $\mu\text{mol/L}$ for females).

Sputum Conversion

Sputum smear was positive in 74.7% of our patients, with the number of new cases being significantly higher than the number of old cases (86.4% versus 46%; $P < 0.001$) (Table 4). Saudi patients who had previous tuberculosis (i.e., old cases) had a lower rate of sputum positivity than did non-Saudi patients ($P < 0.001$). In the first three months after starting chemotherapy, sputum conversion as documented by direct microscopy was achieved in 935 of 1162 patients (80.5%). The remaining 207 patients needed continued hospitalization because of delayed-response resistance or development of drug toxicity. The remaining patients either were unable to produce sputum or were diagnosed by radiological and clinical criteria. The average period of conversion was 43.8 days with no significant differences among the various groups.

Drug Treatment and Resistance

First-line antituberculous therapy with rifampicin, isoniazid, and pyrazinamide with ethambutol or streptomycin was given to 1435 patients. Second-line therapy (including kanamycin, cycloserine, and ethionamide) was then used in 92 patients (5.9%) because drug resistance was either proved or strongly suspected clinically (by delayed conversion). One hundred thirty-one patients either refused treatment, transferred to other institutions, or left against medical advice.

TABLE 4. *Frequency of sputum smear positivity among Saudi and non-Saudi patients.*

Patients	New Cases		Old Cases		Total	
	Smear +/ All Cases	(%)	Smear +/ All Cases	(%)	Smear +/ All Cases	(%)
Saudi	400/458	87.3 ^a	107/289	37 ^b	507/747	67.9
Non-Saudi	561/654	85.8	102/165	61.8	663/819	81
Total	961/1112	86.4	209/454	46	1170/1566	74.7

^a Difference between Saudi and non-Saudi patients is not significant at $P > 0.5$.

^b Difference is significant at $P < 0.001$.

Twenty-six patients had proven drug resistance, with 18 of them resistant to more than two drugs. The pattern of resistance was as follows: isoniazid, 18 (69.2%); rifampicin, 17 (65.4%); streptomycin, 13 (50%); pyrazinamide, ten (38.5%); ethambutol, nine (35.6%); capreomycin, two (7.7%); and ethionamide, two (7.7%).

Fifty-four patients (3.5%) died during the period of the survey, of whom 42 (2.7%) died due to pulmonary tuberculosis.

Discussion

Although the present study was conducted in hospitalized and on referred patients, it nevertheless reflects the general status of active pulmonary tuberculosis in this country. Pulmonary tuberculosis—by affecting mostly adults between 20 and 40 years of age—would have a definite impact on the work productivity due to prolonged morbidity and absenteeism. Such results reflect the recent changes in lifestyle and improved socioeconomic conditions, with children and adolescents unlikely to become affected. BCG vaccination has probably been of some benefit in lowering the rate of disease [7]. Over the last 20 years, BCG vaccination has been given routinely to most newborns in Saudi Arabia.

The male-to-female ratio showed a male predominance, more than has been reported in other studies, and this was even more the case in non-Saudi patients, probably because of the large number of male workers in the country who made up the largest category of our patients [1,2]. The fact that more than one half of our patients were non-Saudi nationals, mostly from other developing countries, is alarming. The vast majority of these men are unskilled manual workers and the women are mostly housekeepers. As with other tuberculosis surveys conducted in the Kingdom, Yemeni nationals constituted the largest number of non-Saudi patients (19.9%) [3]. The representation of other nationals varied from 0.7% to 5.6%, and these generally came from countries with a high prevalence of tuberculosis. Enarson et al [8] showed that immigrants reflect the pattern of tuberculosis in their original country even after a prolonged stay in their new residence [8]. Because of the use of initial screening measures that are usually done upon entry or up to three

months later, it is more likely that these patients had reactivation of previous pulmonary tuberculosis during their stay in the Kingdom, rather than entered with the disease. As a result, such represent a constant source of infection to the community, and in the case of female housekeepers, pose a definite risk to other household members, particularly children and young adults. These results raise the question of how effective are the current screening measures. Without a formal evaluation, our results only imply that such measures are inadequate and must be improved to also identify and deal with inactive cases which can break into active disease [9].

Hemoptysis was more frequently seen in patients who had a previous history of tuberculosis, particularly those with residual lung fibrosis and/or bronchiectasis. When pulmonary tuberculosis is diagnosed fairly early at the start of the disease and effectively treated, resolution is usually complete with very little fibrotic or bronchiectatic changes. However, most of our patients with previous disease had either had no therapy, incomplete therapy, or inadequate drug regimen. Fever was not seen in about 22% of patients and it is important not to let a normal temperature distract one from the diagnosis of active tuberculosis. ESR, which is a nonspecific test, may be useful as an indication of improvement in the general condition, as shown in our study in which the ESR decreased significantly by the time of hospital discharge.

Pyrazinamide was given in a daily oral dose of 1500 mg for the first two months of treatment, and although the uric acid level was found to rise as expected after treatment, none of the patients suffered clinical arthritis, reflecting the rarity of this side effect in this population [10]. A detailed account of other antituberculous drug toxicity will be reported in a separate paper.

The rate of sputum smear positivity was higher in new patients than in those with a history of the disease. This is probably because of a lower load of intrapulmonary bacilli manifesting in a somewhat chronic fashion in the latter cases, compared with the relatively acute or subacute presentation seen in new cases.

The relatively high sputum conversion rate in our patients reflects the efficacy of the drug regimen used, particularly with the addition of pyrazinamide to the initial phase, which is now being given

routinely during the first 2 months of the treatment course in all our patients with active disease [11]. A better conversion rate was not obtained, probably because of the presence of "old" cases that have a higher incidence of resistance.

The occurrence of microbial resistance to all the primary antituberculous drugs including rifampicin is of concern. However, 5.9% of all treated cases developing drug resistance is not a major problem and does not usually interfere with a successful tuberculosis control program [12].

The policy of the Sahary Chest hospital is to admit every patient with a sputum smear positive for acid-fast bacilli. It is well recognized that the majority of cases of active pulmonary tuberculosis can be adequately managed by a properly organized out-patient service, without significant resulting spread of the disease [5]. However, current policy will continue until such services are widely available. We think these services will replace tuberculosis hospitals, mainly because of the presence of effective powerful drugs that produce very good results, as shown in the present study. Convenience to patients and to the treating physician as well as reduced expenses are other factors making such out-patient services a better alternative.

This study, however, has clearly shown that, in a hospital setting where a four-drug regimen is used, patient compliance and side effects are monitored, and health education and contact tracing

are carried out, the outcome can be very encouraging and some of the goals of the National Tuberculosis Control Program can certainly be achieved.

References

1. Shanks NJ, Khalifa I, Al-Kalai D. Tuberculosis in Saudi Arabia. *Saudi Med J* 1983;4(2):151-6.
2. Froude JRL, Kingston M. Extrapulmonary tuberculosis in Saudi Arabia: a review of 162 cases. *King Faisal Specialist Hospital Med J* 1982;2(2):85-95.
3. Andrews RH. WHO assignment report—tuberculosis in Saudi Arabia. WHO/EM/TB 149, 1976.
4. Qawhashmi SA. Prevalence of tuberculosis in Gizan region: a survey report 1984. Chest Hospital, Taif.
5. Aneja KS. WHO assignment report—tuberculosis in Saudi Arabia. WHO/EM/TB 159 and 164, 1982 and 1984.
6. Crofton J, Douglas A. In: Diagnostic standards and classification of tuberculosis. *Respiratory disease*, ed 3. 1981;272.
7. Smith PG. Retrospective assessment of the effectiveness of BCG vaccination against tuberculosis using a case/control method. *Tubercle* 1982;63:1-23.
8. Enarson DA, Ashely MJ, Gryzbowski S. Tuberculosis in immigrants to Canada. *Am Rev Respir Dis* 1979;119:11-8.
9. Bass JR, Farer LS, Hopewell PC, Jacobs RF. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am Rev Respir Dis* 1986;134:355-63.
10. Cullen JH, Early LJA, Fiore JM. The occurrence of hyperuricemia during pyrazinamide-isoniazid therapy. *Am Rev Tuberculosis Pulmonary Dis* 1956;74:289.
11. Combs DL, O'Brien RJ, Geiter LJ. United States Public Health Service. Therapy Trial 21: effectiveness, toxicity and acceptability. *Ann Intern Med* 1990;112:397-406.
12. Crofton J. The prevention and management of drug resistant tuberculosis. *Bull Inter Union against Tuberculosis Lung Dis* 1987;62:1-2;6-11.

IgE-MEDIATED SKIN REACTION AMONG ASTHMATIC CHILDREN IN RIYADH

Abdulrahman Al-Frayh, MD, Facharzt

فحص خمسة وخمسين طفلاً مريضاً (مريضاً بالربو)، تتراوح أعمارهم بين ٦ - ١٣ عاماً، يراجعون عيادة للحساسية عند الأطفال بمجموعة تجارية مكونة من خمس وثلاثين مستأرج بالاستنشاق. صُنفت الخلاصات المستأرجية ضمن مجموعة الطلع، وتشمل الأشجار والأعشاب والحشائش ثم مجموعات الأبواغ الفطرية والحشرات والحيوانات وغيرها من المستأرجات المنزلية. أظهر ٣٥ طفلاً مريضاً (٦٣,٦٪) تفاعلاً جلدياً إيجابياً واحداً أو أكثر. كانت التفاعلات أكثر وقوعاً وشدة في المستأرجات المنزلية والحيوانية وأنواع الطلع. أما التفاعلات الفطرية فكانت أضعف وأقل تواتراً. وهذا يعني أن نسبة الأطفال المربوّن الذين يظهرون تفاعلاً جلدياً إيجابياً أقل منها في البلدان الغربية. وقد يعود ذلك إما لوجود الربو بدون تأتب أو قلة التعرض للمستأرجات المحتملة أو قلة المستضدات المناسبة للمرض في مجموعة فحص الجلد هذه.

Fifty-five asthmatic children aged 6–13 years attending a pediatric allergy clinic were skin tested with a panel of 35 inhalant commercial allergens. The allergen extracts were grouped into pollen including trees, grasses and weeds, fungal spores, insect, animal and other indoor allergens. Thirty-five (63.6%) of the asthmatic children had one or more positive skin reactions. Reactions were most common, and strongest to the indoor and animal panel and to pollens. Fungal reactions were less common and weaker. This represents a lower proportion of skin test-positive asthmatic children than other Western countries. This might relate either to the presence of asthma without atopy, lack of exposure to potential allergens, or lack of appropriate antigens relevant to the disease in the skin test panel.

Identification of allergens in any region is essential for the informed clinical management of allergic diseases. There is little clinical advantage in testing patients for sensitivity to allergens which are not present in their ambient environment. The presence, or absence, of allergens is greatly influenced by various factors such as environmental conditions, patients' living conditions, planting, surroundings, presence of animals, etc.

The present investigation was undertaken to determine the pattern of immediate hypersensitivity reactions to a panel of aeroallergens selected on the basis of studies conducted in the

Riyadh area, which included analyses of air samples for pollen and fungi, and analyses of dust samples from patients' homes [1–4].

Material and Methods

Fifty-five children, 31 boys and 24 girls, attending the Pediatric Allergy Clinic at King Khalid University Hospital, Riyadh, entered the study. They were between 6–13 years of age. All children included were diagnosed as suffering from bronchial asthma based on a detailed history, and a full clinical examination. All children included had been living in the Riyadh area for several years.

All patients were tested with a panel of 35 inhalant commercial allergens, obtained from Hollister Stier ALK and Greer Laboratories. Extracts from pollen grains were standardized with weight:volume ratio w/v: 1:20; fungal spores w/v 1:10, while cat hair (ALK SPT, 5Q, 555), *Dermatophagoides*

From the Department of Pediatrics, College of Medicine, King Saud University.

Address reprint requests and correspondence to Dr. Al-Frayh: Department of Pediatrics (39), College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Accepted for publication 27 August 1990.

farinae and house dust mites mix (ALK SPT SQ 503, 504) and cockroach (Greer Laboratories, SPT, B26) were all purified allergens. These allergen extracts were grouped into pollen, including trees, grasses and weeds, fungal spores, including a range of species identified from spore traps in the region, and insect, animal and other indoor allergens, including dust mite mix, *Dermatophagoides farinae*, dog hair, cat dander, cockroach, cotton flock, sheep wool and horse epithelium. A positive control, with histamine dihydrogen phosphate (1 mg/ml), and normal saline as negative control, were included in the panel for all subjects.

The children had discontinued antihistamines 48 hours before being skin tested. Asthmatic children on long-term corticosteroid therapy were excluded from the study. A detailed history of patients' allergic condition was obtained, and those showing a tendency for "intrinsic asthma" were also excluded.

A standard skin prick method was used, where a drop of allergen solution was applied on the forearm, and the skin pricked through the drop with a lancet (BD-microlance^R [Becton & Dickinson]). Excess solution was then blotted off, and the results were recorded after 15 minutes. A result was considered positive with the wheal diameter measuring 3 mm or more. The results were graded according to the wheal diameter as < 3 mm : negative; 3 mm : mild; 3–5 mm: moderate and > 5 mm : strong.

Results

Thirty-five (63.6%) of the asthmatic children showed one or more positive skin reactions, and 20 patients (36.4%) were skin test negative (Figure 1). Reactions were most common, and strongest, to the indoor and animal panel, and to pollens. Fungal reactions were less common and weaker (Table 1). Among the 35 skin test-positive children, 69 skin reactions occurred to indoor allergen. Thirty of them were significant. A similar distribution was seen with the pollens, but in general the fungal reactions were only mild-to-moderate.

Tables 2, 3, and 4 list the frequency of reactions to individual antigens. By far the most common reactions occurred with cat dander (27 positive), cockroach (16 positive) and cotton flock (10 posi-

tive). Among the grasses, Bermuda grass gave the most frequent reaction, 10 of the 12 being of 5 mm or greater in wheal diameter. In contrast the reactions to the fungal antigens were less common, with *Ulocladium* producing reactions in 6 children and *Alternaria* with *Cladosporium* in 5 and 4, respectively.

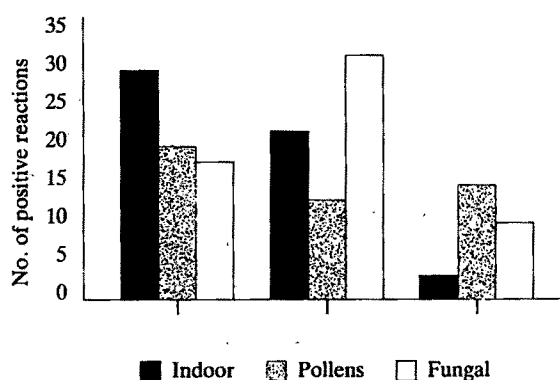


FIGURE 1. Overall pattern of skin test reactivity to aeroallergens in children in Riyadh.

TABLE 1. Overall reactions to aeroallergens in asthmatic children.

Allergens	Degree of sensitivity			Total number positive
	Mild	Moderate	Strong	
Indoor and animal allergens	19	20	30	69
Pollen (tree grass and weeds) allergens	33	14	22	69
Fungal spore allergens	10	15	3	28

– Numbers refer to positive reactions.

– A patient may have more than one positive reaction.

TABLE 2. Skin test reactivity to insect, animal and indoor allergens in asthmatic children.

Allergens	Degree of sensitivity			Total number positive
	Mild	Moderate	Strong	
Cat fur	3	2	22	27
Cockroach	6	7	3	16
Cotton flock	3	5	2	10
Sheep wool	4	2	1	7
Dog hair	2	3	1	6
Dust mite mix	1	1	1	3

TABLE 3. Skin test reactivity to pollen allergens in asthmatic children.

Allergens	Degree of sensitivity			Total number positive
	Mild	Moderate	Strong	
<i>Cynodon dactylon</i> (Bermuda grass)	2	—	10	12
<i>Phragmites communis</i>	3	1	4	8
<i>Poa pratensis</i>	2	3	2	7
<i>Lolium perenne</i>	4	2	1	7
<i>Hordeum sativum</i>	5	2	—	7
<i>Phleum pratense</i>	4	1	1	6
<i>Rumex crispus</i>	6	—	—	6
<i>Zea mays</i>	2	2	1	5
<i>Chenopodium album</i>	3	1	—	4
<i>Acacia</i>	3	—	1	4
<i>Salix caprea</i>	—	3	—	3
<i>Plantago major</i>	3	—	—	3
<i>Artemisia</i>	2	—	1	3

TABLE 4. Skin test reactivity to fungal allergens in asthmatic children.

Allergens	Degree of sensitivity			Total number positive
	Mild	Moderate	Strong	
<i>Ulocladium chartarum</i>	3	2	1	6
<i>Alternaria alternata</i>	3	1	1	5
<i>Cladosporium herbarum</i>	2	2	—	4
<i>Phoma herberum</i>	2	1	—	3
<i>Aspergillus fumigatus</i>	—	—	1	1
<i>Aspergillus niger</i>	1	—	—	1
<i>Rhizopus</i>	1	—	—	1

Discussion

Four major conclusions derive from this study.

Firstly, two thirds of the asthmatic children tested were found to be skin test-positive, with the allergens panel used. This represents a much lower proportion of skin test-positive asthmatic children than in other countries such as the United Kingdom, United States, and Australia, where figures in excess of 90% are the norm. The reason for the lack of positive reaction in the other children relates either to the presence of asthma without atopy, lack of exposure to potential sensitizing allergens, or lack of the appropriate antigens relevant to their disease in the skin test panel.

Secondly, the results show that up to 26 allergens are necessary to detect all the positive reactions in these children, demonstrating the broad range of sensitivities which occur in the Riyadh environment [1-5].

Thirdly, the domestic allergens, particularly cat and cockroach, appeared to be the most important in the test panel, providing frequent and strong reactions. This demonstrates the importance of household dust, and the indoor environment, in producing Type 1 hypersensitivity reactions in asthmatic children [6,7,8-12].

Fourthly, in contrast to reactions in temperate climates, responses to house dust mites are more uncommon (3 positive), reflecting the lack of dust mites in the low humidity of the Riyadh environment [5,13]. However, it is possible that some people who were sensitized by *Dermatophagoides pteronyssinus* or *D. farinae* abroad, and in other parts of the Kingdom, such as Jeddah (where high humidity provides better growth opportunity for house dust mites to thrive), will react to the above allergen extracts. The development of symptoms requires subsequent exposure to specific allergens in the patients' ambient environment. The very low sensitivity to house dust mite antigen in Riyadh is attributable to the negligible existence of these mites. This is supported by our study on indoor allergens in Riyadh [3], and the low humidity in Riyadh could be considered to be an important factor also. Unlike Riyadh, a majority of the western countries have high humidity. The two house dust mite species give frequent positive test reactions, and are major indoor allergens causing bronchial asthma and other perennial symptoms of respiratory allergic diseases.

The high responses to cat antigen have previously been described in Saudi Arabia [5] in patients with rhinitis. While most families indicated that direct cat contact was low, previous reports suggested that cats commonly use stored carpets as resting places, providing the opportunity for cat antigen to be inhaled by children who use these carpets at other times.

The cockroach sensitivity has been implicated as a cause of perennial allergic rhinitis and asthma, and has been found in the rhinitis patients of the study reported above. Bernton and Brown [7] demonstrated a significantly greater frequency of skin test sensitivity in individuals exposed to

environments heavily contaminated with cockroach. Because of the prevalence of this insect in the Saudi environment, we feel it may be the source of a most important indoor allergen, and a major constituent of household dust [7-9].

Currently, we are pursuing studies, with a locally prepared extract, to better define the frequency of cockroach sensitivity in a larger patient environment. The local Arabian cockroach may display different antigenicity from the American and German cockroach, which are the constituents of the skin test extract used [11].

The reactions to grass pollens demonstrate the higher frequency of responses to Bermuda grass, which has previously been demonstrated by Al-Frayh et al. The lower frequency to fungal allergen may reflect the lack of appropriate antigens in the skin test panel, and locally prepared fungal extracts are in the process of development for use to determine more accurately the true allergenicity of these potential aeroallergens in the local environment [3-4]. Some fungal allergens, recorded in our environment [1], are different in their specific nature than those recorded in the waste. *Ulocladium* spp were recorded from both the outdoor, and indoor, environment in Riyadh and are taxonomically related to *Alternaria* spp. In some cases it is difficult to differentiate between the two conidia on air samples slides. However, a comparatively higher proportion of skin reactions with *Ulocladium* also indicates the allergenic importance of individual sensitivities in the region. Comprehensive information on *Ulocladium* will result from a study communication which is now being conducted.

These findings indicate the need for further study in this area, to identify other potential allergens, to develop local allergen testing standards, to determine the clinical contribution of these towards the development of asthma and other allergic conditions, and to examine the

potential for environmental modification in alleviating the prevalence and morbidity of these conditions.

Acknowledgment

The author would like to thank King Abdulaziz City for Science and Technology for financial assistance. This research was supported by funds provided by the KACST (Project AR-7-45).

References

1. Al-Frayh AR, Hasnain SM, Wilson JD, Harfi HA. Fungal allergens in the atmosphere of Saudi Arabia: a preliminary communication. *Ann Saudi Med* 1980;8(4):247-51.
2. Al-Frayh AR, Hasnain SM, Wilson JD. Aeroallergological research in Saudi Arabia. *Inter Aerobiol* 1988;26:20-1.
3. Al-Frayh AR, Hasnain SM. Indoor allergens and atopic response in children in Saudi Arabia. Abstract book of 8th Congress of European Society of Pneumology (SEP) Freiburg (FRG) September 10-14, 1989.
4. Al-Frayh AR, Hasnain SM, Jawadi TQ, Al-Nahdi M. Prevalence of asthma and allergic rhinitis in Saudi Arabia. Abstract book XIVth Congress of the European Academy of Allergy and Clinical Immunology. Berlin (West) September 17-22, 1989.
5. Al-Shalan A, Al-Frayh AR, Reilly H, Al-Husain K, Wilson JD. Inhalant allergens in patients with allergic rhinitis in Riyadh, Saudi Arabia. *Ann Saudi Med* 1989;9(4):331-6.
6. Bann CK, Johnson D, Morgan C, Chang J. The role of immunotherapy in cockroach asthma. *J Asthma* 1988;25(4):205-18.
7. Bernston HS, Brown H. Cockroach allergy. II. The relation of infestation to sensitization. *South Med J* 1967;60:852.
8. Kang F. Study of cockroach antigens as a probable causative agent in bronchial asthma. *J Allergy Clin Immunol* 1976;58:357.
9. Kivily S, Strubar D, Greif G, Schwartz Y, Toplisky M. Cockroach allergen, an important cause of perennial rhinitis. *Allergy* 1989;44:291-3.
10. Mendoza J, Synder RD. Cockroach sensitivity in children with bronchial asthma. *Ann Allergy* 1970;28:159.
11. Rickman PG, Hadayat AK, Turkeltaub NC, Malveaux FY, Baer H. The important sources of German cockroach allergens as determined by RAST analyses. *J Allergy Clin Immunol* 1984;73(5):590-5.
12. Schulaner FA. Sensitivity to the cockroach in three groups of allergic children. *Pediatrics* 1970;45:475.
13. World Health Organization. International Workshop Report: Dust mite allergens and asthma—a worldwide problem. *Bulletin of the WHO* 1988;66(6):769-80.

NURSING: ATTITUDES, PERCEPTIONS AND STRATEGIES FOR PROGRESS IN SAUDI ARABIA

Cynthia L. Jackson, MSN; Rebecca Gary, MSN

تعاين الأقطار الغربية من نقص في الممرضين والمرضات، الأمر الذي سينعكس سلباً على توفر هذا النوع من العمالة في المملكة العربية السعودية في المستقبل نظراً لاعتماد المملكة في هذه الناحية على الأجانب من الممرضين والمرضات. ويعتبر الشباب في المملكة من أغلى مصادر ولكنهم لا يقبلون على مهنة التمريض. ومن هذا المنطلق فقد قمنا بإجراء مسح عشوائي على ١٣٣١ طالباً وطالبة من المرحلتين الثانوية والجامعية للتعرف على مواقف المواطنين ومعلوماتهم العامة عن نظام الرعاية الصحية وإدراكهم لدور الممرض / الممرضة وتوصياتهم حول سعادة مهنة التمريض. فضلت غالبية الذين تم استفتاءهم معالجة المرضى في مستشفيات المملكة وتولي السعوديين تقديم الرعاية التمريضية بدلاً من الأجانب. وكانت النظرة إلى الممرض / الممرضة على أنه شخص مسؤول على تقديم قدر من الرعاية والاهتمام يفوق الخدمة الأساسية للمريض. واعتبر بعضهم عملهم امتداداً لعمل الطبيب دون أن يكون لهم دور في اكتشاف المرض أو الوقاية منه. وقد تبين أن الانطباع السيء عن التمريض كمهنة والقيم الاجتماعية والتقليدية هي العوامل الرئيسية التي تحول دون إقبال السعوديين على مهنة التمريض. وقد تمثلت أهم التوصيات المتعلقة بسعادة التمريض بزيادة الحوافز المالية واستخدام وسائل الإعلام وتخصيص مستشفيات للرجال وأخرى للنساء. وفرت معلومات هذه الدراسة فرصة للتعرف على وجهة نظر الناس الحالية عن التمريض كمهنة محتملة للمواطنين السعوديين، ويمكن أن تشكل في المستقبل دليلاً للجهود الهادفة إلى تطوير مهنة التمريض في المملكة.

Western countries are experiencing a nursing shortage which will impact on future nurse manpower supply in Saudi Arabia because the Kingdom is dependent on expatriate nurses. The young people of Saudi Arabia are the Kingdom's most valuable resources but are reluctant to enter nursing. Therefore, a random survey was administered to 1,131 secondary and university students to determine attitudes and general knowledge of Saudi nationals toward the health care system, perceived role of the nurse and recommendations for improving Saudization of the nursing profession. The majority of those surveyed preferred hospitalization within the Kingdom with Saudi nationals delivering the nursing care rather than expatriates. The nurse was perceived as being a caring person who was responsible for giving more than custodial care. Moreover, the role of the nurse was perceived as an extension of the physician with little or no role in disease detection and prevention. The low image and status of nursing, traditional and social values were identified as major inhibiting factors that affect the Saudi nationals' reluctance to enter nursing. Increasing financial rewards, utilizing the media and segregation of hospitals into male and female were the most frequently cited recommendations to promote Saudization of nursing. Data from this study provided insight into the current perception of nursing as a potential career for Saudi nationals and could provide direction for future concerns in the development of nursing in the Kingdom.

From the Department of Nursing Education and Research, King Faisal Specialist Hospital and Research Centre, Riyadh.

Address reprint requests and correspondence to Cynthia Jackson: King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia.

Accepted for publication 30 August 1990.

Saudi Arabia, a country of vast economic resources, has traditionally relied on expatriates to provide nursing care for its citizens [1]. The current nursing shortage, particularly in the Western world, has dramatically increased the marketability of available nurses which, in turn, has brought

about a proliferation of creative recruitment and retention strategies. The health-care industry in general has responded to this critical shortage of nurses by increasing salaries and benefits, offering flexible work hours and providing tuition-reimbursement plans for those who desire further education [2]. These positive approaches have directly impacted on, and reduced incentives, for Western nurses to consider employment in Saudi Arabia, as well as in other parts of the world. Moreover, despite their advanced knowledge and technological skills, Western nurses are at a disadvantage as care providers for the people of the Kingdom due to language barriers, cultural differences and relatively short-term stay commitments. These factors, along with increased demands for health-care manpower, have necessitated more attention toward attracting Saudi nationals into the nursing profession [3].

In 1407H, a health manpower study estimated that 25,000 nurses were employed in the Kingdom. Of this number, only 8.5% were Saudi nationals, while expatriate nurses accounted for 91.5% of the total population [4]. It is projected that nursing manpower requirements will continually increase over the next 20 years as a result of further expansion in health care facilities, specialized services and natural growth of the population (Figure 1).

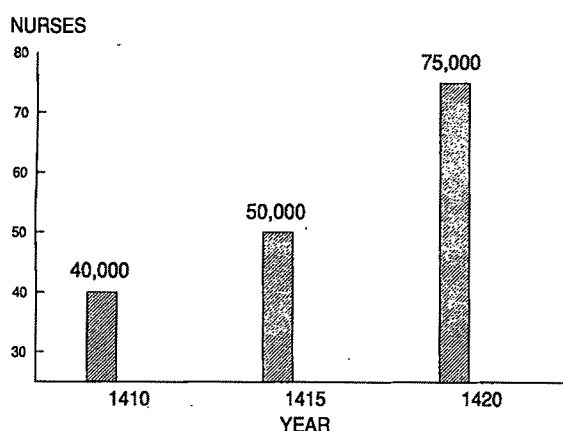


FIGURE 1. Projected nurse manpower requirements. (From Al-Ammari A. Nursing shortage impact on Saudi Arabia: Strategies for the future. Presented at Fourth Annual Health Care Manpower Development Symposium on Nursing: The Future Career. 3-4 October 1989 at King Faisal Specialist Hospital and Research Centre, Riyadh).

Nursing has traditionally been an unacceptable career option for Saudi nationals. This is evidenced by the low numbers of Saudi nationals enrolled in existing nursing programs in the Kingdom. In 1395H (1975G), the national health plan projected a need for 5,000 Saudi nurses by 1399H (1979G). To date, this quota has not been met and only 70 baccalaureate prepared nurses have graduated from either King Abdulaziz University in Jeddah or King Saud University in Riyadh. Graduates from the various technical institutes of nursing, equivalent to nursing assistants in the Western world, currently number approximately 1,000 [5]. The reasons for this reluctance of Saudi nationals to enter nursing are not well documented in the literature, although it has been suggested that the low image/status of nurses, traditional-social values, and inadequate financial rewards are contributing factors [6,7]. If this trend continues, Saudi Arabia must continue to rely upon expatriate nurses, which may not be in the best future interest of its citizens.

Unless specific strategies are developed, Saudi Arabia may suffer from diminishing nurse manpower resources at a time of increasing health care demands. As a step toward the goal of addressing future strategies, this study was conducted at the request of the hospital administration for the Fourth Annual Health Care Manpower Symposium entitled, "Nursing: The Future Career", held at King Faisal Specialist Hospital and Research Centre, 3-4 October 1989.

The Saudi youth are the Kingdom's most valuable resources and are fundamental in reversing current trends. Their attitudes and career choices will determine the nature of the health care delivery system in the future. Therefore, a random survey of secondary and college-aged Saudi nationals was conducted in order to answer the following questions:

1. What is the knowledge, attitude, and perception of Saudi nationals toward the health care system in general and the nursing profession in particular?
2. What current factors influence the entry of Saudi nationals into the nursing profession?
3. Which incentives or rewards would encourage Saudi nationals to enter nursing?

Material and Methods

A 25-item questionnaire consisting of 21 closed-ended, i.e., selection of an answer and 4 open-ended questions, wherein the respondent could write in an answer, was used as the instrument for this study. The questions were subcategorized into the following groups for analysis purposes:

1. General knowledge of and attitudes toward the health care system and the nursing profession
2. Perceptions of the role of the nurse
3. Image/status of nursing
4. Traditional-social values which affect Saudi nationals' entry into nursing
5. Recommendations for Saudization of nursing

The questionnaire was translated into Arabic and reviewed for content and clarity by a graduate nursing student enrolled at King Saud University and by members of the Human Resources Department (HRD) at King Faisal Specialist Hospital & Research Centre (KFSH&RC).

Study Population

The questionnaire was randomly distributed to male and female students attending secondary public school systems and to secondary schools sponsored by the Ministry of Defense and Aviation in the Riyadh area. The selection of public schools was designated by members of the Human Resources Department (HRD), based on location of the school and the socioeconomic status of the students served. Every attempt was made by the HRD to equally distribute the sample population in relation to socioeconomic status in order to get a more generalized view of all strata of Saudi citizens. In addition, the male and female campuses of King Saud University in the Riyadh area who were not already committed to a health-related profession were included in the sample.

Rationale for Selection

This target population was selected because these young men and women are the present resources and future leaders of the Kingdom. Second, it was felt that a population not committed to any health care profession might contribute fresh

insight into the attitudes, knowledge, and perceptions of the Saudi population in general. Third, due to the fact that Saudi males are the leaders of the nation, as well as the family, the researchers felt that it was particularly important to include males in the target population. Finally, the female researchers' ability to access the female population was far easier to accomplish than accessing the male population, which was not possible without the assistance of male members of the Human Resources Department.

Data Analysis

The data was analyzed using descriptive methods by the Human Resources Department personnel at KFSH&RC.

Results

The questionnaires were randomly distributed by the researchers and members of the Human Resources Department at Riyadh area schools and King Saud University. A total of 1131 questionnaires were completed. The sample was categorized according to sex and level of education (Table 1).

General Attitudes and Knowledge

Sixty two percent (62%) of the respondents had little or no background knowledge of nursing. This was supported by the fact that only 30% of

TABLE 1. Demographic data for sample population.

Educational level	Male No. (%)	Female No. (%)	Total
University	171 (33)	351 (67)	522
Secondary	173 (28)	436 (72)	609
Total	344 (30)	787 (70)	1131

TABLE 2. Summary: General attitudes and knowledge toward health care system and nursing.

Attitudes and knowledge	Yes (%)	No (%)
Awareness of nursing shortage	30	70
Nurses are essential	96	4
Patients get better due to nursing care	89	11
Hospitalization within the Kingdom	83	17
Saudi nationals as nursing care providers	70	30

the sample indicated an awareness that a worldwide nursing shortage currently exists.

Ninety six percent (96%) of the research sample agreed that nursing is essential to any health care system and the majority (89%) agreed that the patients' health improves because of nursing care.

Eighty three percent (83%) preferred to be hospitalized within the Kingdom rather than seeking health care abroad, and they preferred that Saudi nationals deliver the nursing care (70%) as compared to expatriate nurses (Table 2). When asked if nursing was a possible career option, 36% of the respondents indicated they would consider nursing in the future as a career.

Perception of Nursing Role

This sub-category consisted of nine questions related to various functions considered within the domain of nursing practice. The results are summarized in Table 3. Briefly, the nurse was perceived by the majority of the population as a caring person who is expected to provide more than custodial care. Nursing was not viewed as an autonomous profession, but more as an extension of medicine with the nurse having little or no independent decision making role. Moreover, results indicated that the nurse is perceived as having no role in the detection and/or prevention of disease.

The majority of the respondents (27% = 1-2 years; 41% = 2-4 years) indicated that the nurse should have a minimum of 2 years formal education (Figure 2). Knowledge of diseases, religion and culture, provision of emergency care, and adequate preparation in the delivery of technical skills, were all viewed as part of the nurses' responsibility in providing patient care. In regard

to health education, the nurse is perceived as being an appropriate source of information regarding practices which will achieve and maintain "good health." However, they believed that nurses had no role in disease prevention which is somewhat contradictory.

Image and Status of Nursing

Participants were asked to numerically rank a set of occupations according to perceived status (Figure 3).

In relation to image and status, teaching, military service and business were ranked as the most attractive occupational choices. Nursing was ranked sixth out of thirteen career choices. When compared with other health professions, nursing was numerically ranked lower than pharmacy, but higher than other health-care occupations such as

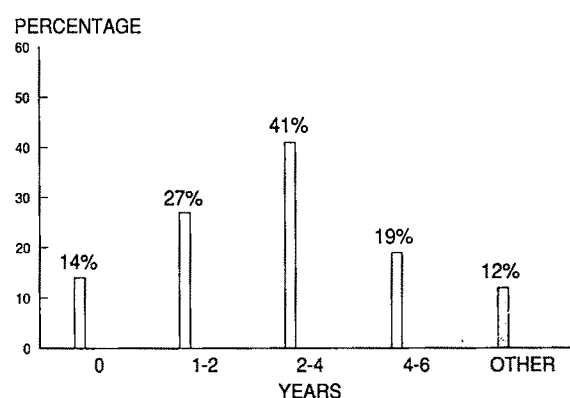


FIGURE 2. Educational requirements to become a nurse as perceived by sample population.

TABLE 3. Summary: The role of nursing as perceived by sample population.

Role	Agree (%)	Disagree (%)
Caring person	93	7
Provision of more than custodial care	78	22
Knowledgeable about religion and culture	87	13
Health educators regarding "good health"	72	28
Need for technical skills	78	22
Extension of physician	76	24
Disease detection and prevention	37	63

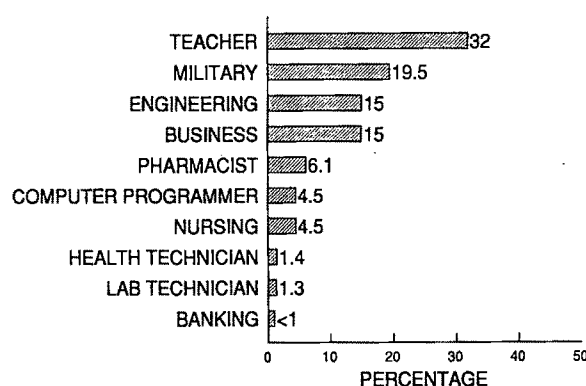


FIGURE 3. Numerical ranking of occupations according to perceived status.

laboratory and x-ray technicians and dental hygienists. The researchers assumed that physicians would be ranked higher in image and status than nurses; and therefore medical practice was not included as a career choice.

In response to the question regarding whether social class should influence the decision as to who should enter the nursing profession, 57% agreed while 43% disagreed. Specific questions aimed at ascertaining which members of what level(s) of society should enter nursing were not addressed by this study.

Traditional-Social Values

Current traditional-social values of Saudi society were perceived as important, influencing factors in choosing nursing as a career. Sixty nine percent (69%) of those responding indicated that they would support a family member who chose to enter the nursing profession. Of the 31% who would not, 72% cited "social" reasons as primary inhibiting factors. These reasons included undesirable work hours, traditional roles of women in society and the non-segregated work environment that currently exists in most hospitals. Salary was not indicated as a major factor in lack of support of one's family member in the choice to enter nursing, as only 5% of respondents listed salary as a concern. Segregation of hospitals into male and female divisions would provide one major incentive for Saudi nationals to enter the nursing profession, as 80% (N = 802) of respondents stated that nursing would be a viable career option if this occurred.

Since a great deal of emphasis is placed on marriage, a question was asked regarding whether or not the participants would consider marrying a nurse. Sixty four percent (64%) indicated they would not marry a nurse. "Social" reasons were cited as the major deterrent in this choice. The specific social reasons indicated were the same as those listed previously in response to reason for not supporting a family member's choice to become a nurse. Again, only 5% viewed financial incentives as a factor for their response to this question. The reasons for this are not well understood, i.e., lack of knowledge regarding salaries or financial rewards not a concern. Further research on this topic may provide clarification on this matter.

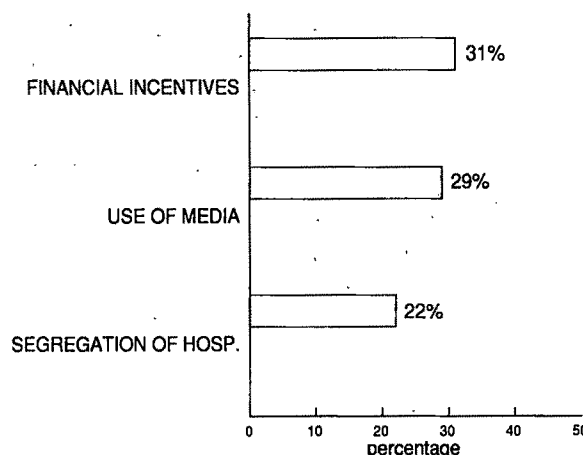


FIGURE 4. Strategies for improving the Saudization of nursing as recommended by sample population.

Recommendations for Saudization of Nursing

Fifty-nine percent (N = 667) of the sample responded to the question regarding factors that would most likely increase Saudization of nursing. Improving financial incentives/rewards (31%), use of media to improve the overall image of nursing (29%), and segregating hospitals (22%) were cited most frequently as measures that would promote Saudization of the nursing profession (Figure 4).

Discussion

Saudi Arabia currently has "state of the art" medical care and health-care facilities to offer its citizens. There is no longer a need for Saudi citizens to seek health care abroad, and according to this study, hospitalization within the Kingdom is preferred. Moreover, Saudi nationals are in preference to be the nursing care providers as compared with expatriate nurses. This is problematic, however, since nursing is considered a less than acceptable career choice for the majority of Saudi nationals. Enrollment in the Kingdom's established nursing institutes and colleges suggests this trend is not likely to improve in the near future. Unless specific measures are adopted to attract Saudi nationals into nursing, the quality of patient care, as well as the accessibility to health services by the people, could be threatened in the future.

The results of this study indicate that nursing is perceived relatively low in status in comparison to other occupational choices. This is somewhat congruent with the image of nursing in the western

world, although changing due to the acute shortage. The low image of nursing as a predominantly female occupation has contributed to the existing shortage with females choosing and being recruited into more lucrative occupations, such as business, law, medicine, etc. Reluctance to choose nursing as a career in Saudi Arabia is based on this perception of low image along with current traditional-social values of the society. Financial concerns were not considered a major deterrent for entering nursing, although recommendations for improving Saudization included increasing financial rewards.

Limitations of the Study

The nature of Saudi society prohibits easy access to its citizens. Moreover, the logistics and manpower required to solicit responses outside of the Riyadh area and/or undertake a Kingdom wide survey were not feasible at the time the study was conducted. Any generalizations of this study to the Saudi population, therefore, must be made with caution.

Implications and Recommendations

Data from this study provided insight into the current perception of nursing as a potential career for Saudi nationals and could provide direction for future concerns in the development of nursing in the Kingdom.

First, it is important for the people of Saudi Arabia and leaders of health-care policy to determine if the best interests of the citizens will be served by adopting a western perception of the nursing profession. Levels of practice, educational preparation, licensure and credentialing are issues that should be addressed and appropriately integrated into the health-care expectations of the Saudi citizens. From this, a unified national nursing education policy could emerge that would identify what nurses need to know in order to deliver care within the context of Saudi society.

Second, the resources need to be identified that can be utilized to effect change, if change is desired. Religious leaders, leaders of national policy, Arabic media and the school systems are all potential resources toward this effort. In papers presented at the Fourth Annual Health Manpower Symposium, Dr. Nasser from King Abdulaziz University and Major Rashid Aba

Alkhail, M.D., from Security Forces Hospital supported that nursing practice is consistent with Islamic teachings. They went on to state that the historical development of nursing could be traced during the early period of Islam. Support by religious leaders for Saudi nationals to enter nursing could promote enthusiasm and reduce the traditional barriers in selecting nursing as a career option.

The Arabic media could play a major role in helping to reverse the current negative image of the nursing profession. The nurse portrayed in a manner that is consistent with religious and traditional-social mores of Saudi society would encourage a more positive view of nursing that is consistent within the framework of societal values. Educating the public regarding the expanded role of the nurse in patient care delivery might encourage increased interest in these areas, i.e., nurse practitioner, educator, administrator. The media, particularly television and newspapers, were identified as major resources to promote Saudization by our research sample. For example, the recent location of kidney transplant recipients broadcast over television brought the two young boys rapidly to King Faisal Specialist Hospital and Research Centre when all other communication contact attempts failed. Saudis do watch television and have limited options for programming. A series on nursing could be most effective.

The youth of Saudi Arabia are a captive audience when they are enrolled in the elementary and secondary school system. Saudi nurses could be utilized as health educators in the school system as well as in an expanded role capacity such as nurse practitioner. Both of these functions could serve as positive role models for students who may wish to pursue nursing as a future career. The role of the nurse/teacher could be of particular value when health concerns of the adolescent are addressed. Currently, the Kingdom has launched a nationwide campaign to promote a drug-free society. Nurses can make valuable contributions to such efforts because of their psychosocial and physiological knowledge base.

Third, one of the primary responsibilities of the male population is to provide support to the family. In order to promote the acceptance of nursing as a career option for men, increasing financial rewards may be necessary. Although financial

concerns were not listed as primary reasons for not choosing nursing as a career, it was considered a major strategy for promoting Saudization of nursing. The leaders of national policy could help toward this goal by improving financial incentives to enter nursing. Increased stipends while studying nursing, as well as improved salaries upon graduation, could increase motivation to choose nursing as a field of study.

According to the data, segregation of sexes in the work environment is a major incentive that would attract more Saudi nationals into nursing. Practical consideration may need to be given as to how this could be accomplished in order to provide a work environment more reflective of traditional-social norms. It is recognized this would be a major dilemma for the health-care leaders of the Kingdom. Segregation of hospitals would pose enormous financial and administrative challenges. In the long-run, however, it may be more cost-effective for several reasons. Removing traditional-social barriers would attract more Saudi nationals into nursing as our data suggest, thereby reducing the economic constraints of an expatriate work force. In addition, care could be provided by those who are most suitable from a traditional, cultural and religious standpoint. Work hours, a major deterrent for choosing nursing, may not be as problematic if the hospitals were segregated.

During the transition period of Saudization in nursing, expatriate nurses could be utilized as consultants, similar to that of the medical profession. Advanced clinical knowledge and expertise could be disseminated through perceptorships and educational programs. Preparation for extended roles

such as Administrator, Educator and Practitioner could be facilitated with expatriate nurses currently fulfilling these roles.

In conclusion, the nursing shortage is real, and according to predictions, will continue to grow into the next century. Nurses are, and will continue to be, a valued commodity as they become more limited. The costs of recruiting expatriate nurses may become economically prohibitive for Saudi Arabia in the future. Also, the most expensive health-care provider may not be the best or most appropriate for delivering care to the citizens. The challenge that lies ahead, therefore, is to work at developing a unique, cost-effective health-care delivery system that makes the best use of the current and projected resources available.

References

1. Sebai Z. Health services in Saudi Arabia. Part 1: an overview. *Saudi Med J* 1987;8(6).
2. Miller A, Bradburn E. Seeking an Rx for nurses: as shortages grow, hospitals recruit harder. *Newsweek* 1989; July 10:32-3.
3. Al-Swailem AR. Assessing health care delivery in Saudi Arabia. *Ann Saudi Med* 1990;10(1):63-8.
4. Ministry of Health, Kingdom of Saudi Arabia. Annual Statistical Report. Riyadh (1987, 1407H).
5. Brown BJ. Nursing administration in Saudi Arabia. In: Henry (editor). *International administration of nursing services*. Philadelphia: Charles Press, 1989:59-66.
6. Aba-Alkheil R. Saudization of nursing: difficulties-solutions. Presented at Fourth Annual Health Care Manpower Development Symposium on Nursing: The Future Career. 3-4 October 1989 at King Faisal Specialist Hospital and Research Centre, Riyadh.
7. Nasser K. Social factors and their impact locally on nursing as a profession. Presented At Fourth Annual Health Care Manpower Development Symposium On Nursing: The Future Career. 3-4 October 1989 at King Faisal Specialist Hospital and Research Centre, Riyadh.

Case Reports

GLUTEAL NECROSIS WITH ANO-GLUTEAL FISTULA: A RESULT OF UMBILICAL ARTERY CATHETERIZATION

A. Latif Al-Arfaj, Fachartz, MD; Mohammed S. Khwaja, MD

Since its first introduction in the Boston Hospital for Women [1] in 1961, the umbilical artery catheter (UAC) has been increasingly in use for diagnostic, investigative, monitoring and therapeutic purposes [2].

A multitude of complications such as peripheral embolization leading to loss of an extremity or part of it, transverse myelitis, renovascular hypertension, intestinal necrosis, gluteal skin with or without muscle necrosis and occult hemorrhage have been reported [3,4]. Blanching of an extremity or part of it can be caused by vasospasm induced by UAC. Air embolism and infection ranging from bacterial colonization, bacteremia to sepsis, osteomyelitis, septic arthritis and mycotic aneurysm have been described [4]. Urbach et al have also reported two cases of refractory paradoxical hypoglycemia due to misplaced UAC next to the pancreatic artery [5].

A combination of gluteal necrosis with ano-gluteal fistula and pyogenic arthritis as presented in the following report has not so far been documented in the literature.

Case Report

A full-term neonate weighing 2900 g was delivered vaginally on 4 December 1989 to a mother gravida 6, para 5, and one abortion with no history of abnormalities. The liquor was meconium stained. The baby looked very pale, hypotonic, tachypneic and cyanotic. Apgar score was 5 and 6 at 1 and 5 minutes and 6 at 10 minutes; temperature 35.9°C; pulse 129 per minute; respiratory rate 60/min; blood pressure 40/28 torr. Patient

responded only to painful stimuli with weakly elicited Moro reflex. Blood gases: pH, 6.98; PCO₂, 51, PO₂, 32; bicarbonate, 11; base excess -18. Oxygen saturation was 33%. Complete blood count showed: Hb, 2.4 mmol/L with hematocrit of 13; MCV, 116.7; MCH, 2.17; MCHC, 18.5; and platelet count was 205,000. The WBC was 11.4 with 14% segs, 18% bands, 66% lymphocytes, 2% eosinophils and a reticulocyte count of 1.7%. Kleihauer test was positive indicating feto-maternal transfusion. TORCH screening was negative.

At the age of 6 hours she developed convulsions requiring a high dose of phenobarbital as well as dilantin. CT scan showed ventricular dilatation and a hypodense area suggesting cerebral anoxia. The EEG showed a focus of abnormal activity in the right hemisphere.

On the third day she had "bluish discoloration" of her left thigh. The umbilical catheter was then removed. There was, however, no improvement in the ischemia, which ultimately progressed to frank necrosis. On the seventeenth day she started discharging fecal matter through the necrosed area. Two days later she was referred to us with a diagnosis of gluteal necrosis with "ano-gluteal" fistula. She subsequently underwent debridement of the necrosed tissue—all three gluteal muscles were dead. A hole in the posterior anal wall was identified, and confirmed by a probe, about 1½ cm above the anal verge (Figure 1). The sacroiliac and hip joints were open to the necrotic tissue. A right transverse colostomy was fashioned. After the infection had been controlled and the nutritional status improved, the gluteal surface was skin-covered with a rotational contra-lateral gluteal flap (Figure 2). The colostomy was closed at the age of 3 months, with subsequent normal bowel function. The movement of the hip joint has remained limited in all directions including rotation, and is being followed up by the pediatric orthopedic service.

From the Department of Surgery, Division of Pediatric Surgery, College of Medicine and Medical Sciences, King Faisal University, Dammam.

Address reprint requests and correspondence to Dr. Al-Arfaj: Thogbah, P.O. Box 20325, Al-Khobar 31952, Saudi Arabia.

Accepted for publication 12 August 1990.

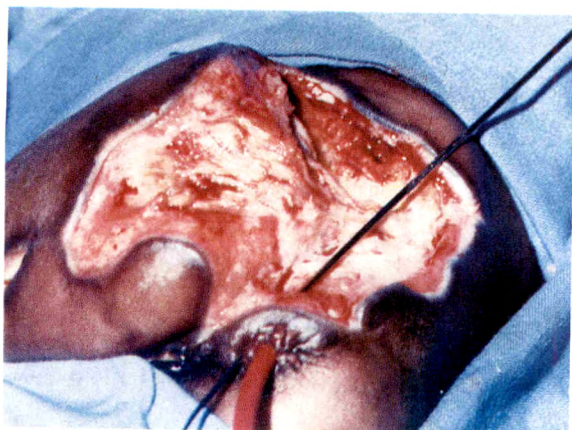


FIGURE 1. Patient in right decubitus position after excision. The probe demonstrates the site of the fistula.

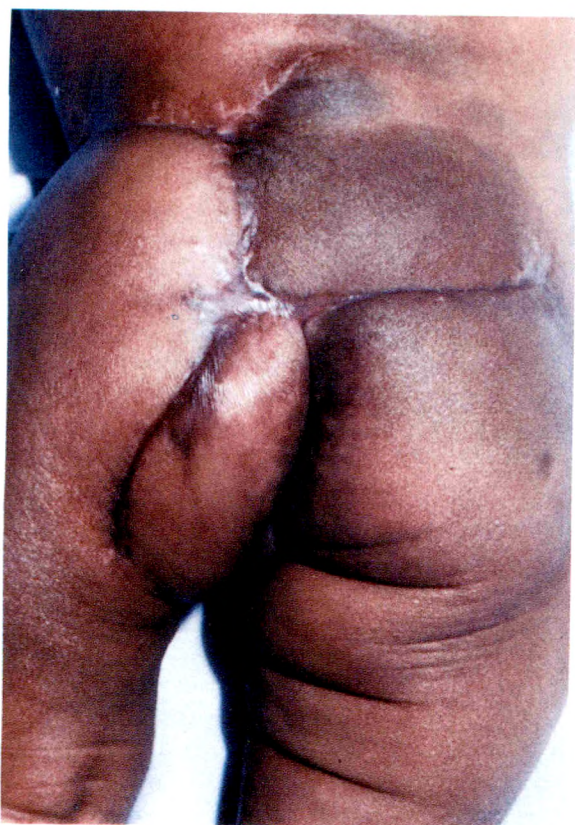


FIGURE 2. The healed gluteal region after contralateral rotational gluteal flap.

Discussion

A host of risk factors has been found responsible for the development of complications resulting from ischemia. Some of the important factors include low birth weight, low flow states, hyper-

viscosity/hypercoagulability, sepsis [6] and abnormal pH of the infusate as well as the method of UAC insertion [7]. Likewise the type of catheter appears to be a factor, with those with side holes, small gauge, and those made of polyvinyl chloride being at greater risk [4,8–10]. The level of catheter placement in the aorta is controversial. Seibert et al and others recommend positioning the catheter just above the aortic bifurcation [10–12], although the formation of thrombi in this position is more likely [13]. The complications of catheters placed higher in the aorta although less frequent involve the visceral vasculature and are more life-threatening [10–12]. The addition of calcium to the infusate as well as birth asphyxia with its low flow state as evidenced by a high rate of neurologic sequelae significantly increase the risk of clot formation [10–12] as observed in our case.

Clinical monitoring should include registration of peripheral pulse, skin temperature, and color change [4,11]. The color change, however, may not be a reliable indicator in a dark-skinned subject. Besides, attention should be directed to signs of systemic manifestation of on-going thrombosis and thrombolysis, metabolic acidosis, hypertension, etc [12]. There may be poor correlation between clinical findings, and the development of thrombosis as a precursor of major complication [10,13]. Therefore, the most effective way of prevention is close monitoring of all infants at high risk. Other prophylactic measures are frequent reassessment of the need for UAC, the introduction of alternatives such as percutaneous peripheral cannulation, doppler and oscillometric techniques and the use of silastic material whenever possible [4]. If local or systemic manifestation is suspected, an immediate diluted contrast study via the catheter itself is performed. Otherwise radionuclide scanning or sonography is sufficient to confirm or exclude the diagnosis [12,14].

In case of vasospasm, the catheter must be removed at once [11]. However, the ischemic process may progress to frank gangrene [4], which usually corresponds to the supply area of the occluded artery [15,16]. The occlusion of the inferior gluteal artery will produce skin necrosis only [15,17,18], but if both gluteal arteries become occluded, there will be total necrosis of skin and muscles [19]; in addition, neurologic dis-

orders involving the sciatic nerve may occur [20]. The extent of necrosis in our case suggests that many branches of the internal iliac artery, in particular arteriae gluteales, rectalis media, rectalis inferior and pudenda interna were affected.

The probable mechanism of fistula formation in this infant was erosion of the partially ischemic anal canal by infection as a result of delayed debridement. Likewise the joint involvement could have been avoided by early excision of the necrotic material.

References

1. Nelson NM, Prodhon LS, Cherry RB, et al. Pulmonary function in the newborn infant: perfusion estimation by analysis of arterial-alveolar carbon dioxide difference. *Pediatrics* 1962;30:975-89.
2. El-Shafie M, Steward R, Klipper CH. Transumbilical aortography in newborn infants for non-cardiac diagnosis. *J Pediatr Surg* 1976;11:517.
3. Anonymous: Umbilical catheter risks. *Pediatrics Rev* 1983;4:278-9.
4. Caeton AJ, Goetzman BW. Risky business: umbilical artery catheterization. *Am J Dis Child* 1985;139:120-1.
5. Urbach J, Kaplan M, Blondheim O, Hirsch HJ. Neonatal hypoglycemia related to umbilical artery catheter malposition. *J Pediatr* 1985;106(5):825-6.
6. Wigger JH, Bransilver BR, Blanc WA. Thrombosis due to catheterization in infants and children. *J Pediatr* 1970;76:1-11.
7. Marsh JL, King W, Barrett C, et al. Serious complications after umbilical artery catheterization for neonatal monitoring. *Surgery* 1975;110:1203-8.
8. Hecker JF. Thrombogenicity of tips of umbilical catheters. *Pediatrics* 1981;67:467-71.
9. Wesstrom G, Finstrom O, Steppert G. Umbilical artery catheterization in newborns: thrombosis in relation to catheter type and position. *Acta Pediatr Scand* 1979;68:575-81.
10. Seibert JJ, Taylor BJ, Williamson SL, et al. Sonographic detection of neonatal umbilical artery thrombosis: clinical correlation. *Am J Radiol* 1987;148:965-8.
11. Bush GH, Dangel P, Rickham PP. Umbilical arterial catheter. In: *Neonatal Surgery*. London, Boston: Butterworths and Company, 1978;46.
12. Krueger TC, Neblett WW, O'Neil JA, et al. Management of aortic thrombosis secondary to umbilical artery catheters in neonates. *J Pediatr Surg* 1985;20:328-32.
13. Makrohsy ST, Levine RL, Blumhagen JD, et al. Low positioning of umbilical artery catheters increases associated complications in newborn infants. *N Engl J Med* 1978;299:561-4.
14. Merten DF, Vogel JM, Adelman RD, et al. Renovascular hypertension as a complication of umbilical artery catheterization. *Radiology* 1978;126:751-7.
15. De Curtis M, Mastropasqua S, Paludetto R, et al. Gangrene of the buttock: a devastating complication of the infusion of hyperosmolar solutions in the umbilical artery at birth. *Eur J Pediatr* 1985;144:261-2.
16. Benninghoff A, Goertler K. *Lehrbuch der anatomie des menschen*. Urban and Schwarzenberg. Muenchen, Berlin 1964;2:510-11.
17. Cutler VE, Strecher GS. Cutaneous complications of central umbilical artery catheterization. *Arch Dermatol* 1977;113:61-3.
18. Mann NP. Gluteal skin necrosis after umbilical artery catheterization. *Arch Dis Child* 1980;55:815-7.
19. Rudolph N, Wang HH, Dragutsky D. Gangrene of buttock: a complication of umbilical artery catheterization. *Pediatrics* 1974;53:106-9.
20. Purohit DM, Abner HC, De Vito PC. Gluteal necrosis with foot drop. *Am J Dis Child* 1978;132:897-9.

ABDOMINAL COCOON IN A PREGNANT WOMAN: A CASE REPORT AND REVIEW OF THE LITERATURE

Kamal I. Ali Gharaibeh, FRCS(Glas); N. A. Morad, MD, PhD;
E. Sunna, MRCOG

Encasement of a variable length of small intestine by a fibrous membrane, usually presenting as intestinal obstruction, and/or, an abdominal mass, was first described as an abdominal cocoon in 1978 [1]. A search of the literature has revealed thirteen cases [1-4], and an additional case was reported as peritoneal encapsulation [5], which is more likely to have been an abdominal cocoon. This results in a total of fifteen cases, including our own, are discussed in this study.

Case Report

A 26-year-old female, who was 25 weeks pregnant, was admitted to this hospital complaining of colicky abdominal pain in the right iliac fossa of two days duration, accompanied by nausea without vomiting.

She gave a history of recurrent attacks of similar, but less severe, pain during the five years prior to this attack. Her menstruations were reported as very painful, but regular. There was no other relevant medical or drug history. On examination her pulse was 88 per minute, her temperature was 37.1°C, and abdominal examination revealed tenderness in the right iliac fossa. The size of the uterus corresponded with the date of her last menstrual period 25 weeks ago. Fetal heart sounds were regular, and 135 beats per minute. No abnormality was detected on routine urine testing. The WBC was 14000 cells per cubic millimeter. The pain became more severe in the fol-

lowing two hours; her pulse rate rose to 94 beats per minute; her temperature rose to 37.5°C; she vomited; and her WBC rose to 16000 cells per cubic millimeter. It was felt that an appendectomy should be performed.

However, through a right McBurney incision, the appendix looked normal. The right fallopian tube, ovary and the uterus also showed no sign of gross pathology. When the terminal ileum was brought out of the wound, a membrane was found to be encasing the distal 30-40 cm of it, sparing only the ileocecal junction area with two openings in the membrane for the afferent and efferent small intestine, which was distended proximally. The pelvic surface of the sac, which was thicker than other surfaces, was studded with minute brownish spots. The membrane was dissected off the intestine, and its mesentery, with slight difficulty. Then the appendectomy was performed.

Postoperative progress was uneventful. Three months later the patient had a normal delivery, giving birth to a healthy female infant. She reported that her periods were not as painful as before, and her last surgical and obstetric exam, six months later, revealed no abnormalities.

Pathology

The appendix was normal. Sections taken from the tissue submitted for histopathology showed fibrovascular tissue admixed with mature adipose tissue. No inflammatory cells were present. However, selective sections taken from the scattered minute brown foci revealed glandular structures lined by a single layer of low columnar epithelium and surrounded by large cells with distinct borders and granular pink cytoplasm (decidua-like cells). There were few foci of hemosiderin laden macrophages (Figures 1, 2). No trophoblastic tissue nor chorionic villi were identified.

From the Departments of General Surgery (Dr. Gharaibeh), Pathology (Dr. Morad) and Obstetrics and Gynaecology (Dr. Sunna), Jordan University of Science and Technology, Princess Basma Teaching Hospital, Irbid, Jordan.

Address reprint requests and correspondence to Dr. Gharaibeh: P.O. Box 1154, Irbid, Jordan.

Accepted for publication 5 August 1990.

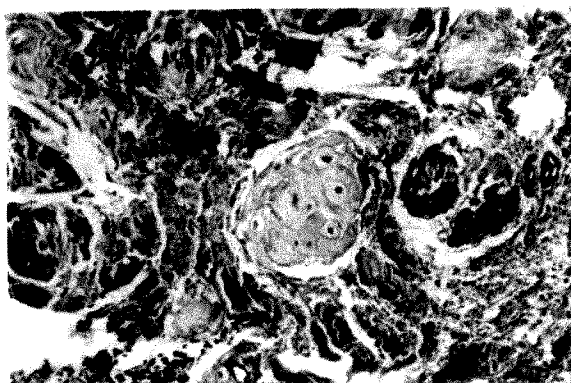


FIGURE 1. Nest of decidua-like cells entrapped within the fibrous capsule. (Hematoxylin-eosin stain; original magnification $\times 150$.)

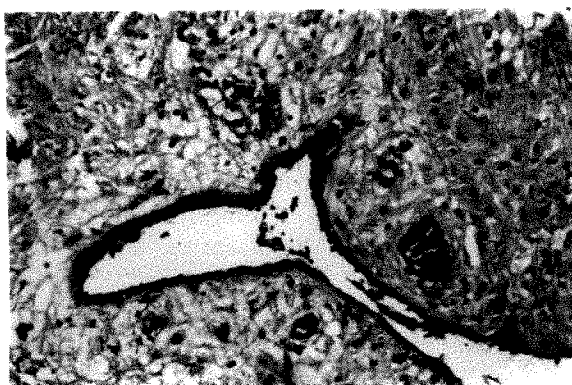


FIGURE 2. Glandular structure, lined by low columnar epithelium and surrounded by clusters of decidua cells. (Hematoxylin-eosin stain; original magnification $\times 150$.)

Discussion

Abdominal cocoon is a condition that occurs in young females and is characterized by the encasement of a variable length of the small intestine by a membrane, which usually presents with a small intestinal obstruction and/or abdominal mass.

It was first described by Foo et al in 1978 [1] who reported ten cases of young postmenarchal females (Table 1). Based upon the age and sex of the patients, being postmenarchal females, and the histology of the membrane which may suggest the possibility of viral infection, Foo wondered if this condition could be due to retrograde menstruation superimposing subclinical primary viral peritonitis leading to chronic inflammation and the formation of a cocoon.

Foo however could not relate his postulation to his patients. Furthermore, three more cases were reported later [2-4], in which two of them [2,3]

occurred in premenarchal females (Table 1), which were not in the favor of his postulation.

The pathology findings in our case with the decidua-like cells, and the absence of trophoblastic tissue, excludes the possibility of retrograde passage of products of the intrauterine conception, and could be due to decidual changes of pregnancy.

Abdominal cocoon must be differentiated from peritoneal encapsulation, which is a rare condition characterized by the presence of an accessory peritoneal membrane. This membrane lies posterior to the greater omentum, separating it from the small intestine, and is attached superiorly to the transverse mesocolon, laterally to the ascending and descending colon, and caudally to the posterior parietal peritoneum of the pelvic rim. This condition was first described in 1868 [6], subsequently nine more cases have been reported [2,5,7-11]. It is generally agreed that this condition is congenital, and is due to an abnormal return of the midgut when the peritoneum is withdrawn with it to the peritoneal cavity, in the early fetal life.

All of the peritoneal encapsulation cases were diagnosed at autopsy, or during operations for unrelated conditions. Only one case was presented with intestinal obstruction [7]. All of the cases were over fifty years of age, except one [5], which, we agree with the others [2], was an abdominal cocoon, and not an encapsulation (Table 2). Thus, the number of abdominal cocoons are fifteen, including ours, and there are nine cases of peritoneal encapsulation.

Other diagnostic possibilities that should be excluded are tuberculosis, postoperative fibrosis, and sclerosing peritonitis [12], which have been reviewed lately, and includes a variety of conditions under its heading. These conditions are practionol therapy [13-15], carcinoid syndrome, familial Mediterranean fever, blunt abdominal trauma, abdominal cocoon, and asbestos exposure. In the medical history, and the pathological findings of our patient, there was no evidence to suggest any of the above conditions.

The treatment of this condition should be simple, and entails an excision of the membrane. We prefer to remove the appendix, especially if the incision is that of an appendectomy, and also the possibility of later appendicitis, which could be difficult to treat if any adhesions are present.

TABLE 1. Summary of cases of abdominal cocoon.

	Age	Sex	Presentation	Findings	Operation	Pathology
Foo ¹	13-18	Female	5 cases had acute small intestinal obstruction, 2 cases subacute intestinal obstruction, 3 cases with abdominal mass and admitted to the GYN ward	Fibrous capsule involving variable lengths of the small intestine	Rt. hemicolectomy in one case, ileocolic bypass in another cases, Nobél's plication in the third case, 7 cases had freeing of these; 5 had appendectomy	Seven cases were examined showing thick smooth membrane, 5 of them had a covering of mesothelial cells in local areas with mild vascularization and a focal collection of lymphocytes. Lymph nodes showed non-specific reactive sinus histiocytosis
Rao et al ³	4	Female	Acute small intestinal obstruction	Thick membrane sparing only the proximal 6 inches of the small intestine and encasing the rest of the small intestine	Removal of the capsule and freeing the intestine	Fibrocollagenous material
Marino and Adelusi ⁴	17	Female	Abdominal pain with an abdominal mass	Capsule encasing the distal 4 feet of the small intestine and adhesion with the parietal peritoneum	Excision of the capsule	Thick fibrocollagenous tissue, collection of inflammatory cells
Sieck et al ²	14	Female	Acute small intestinal obstruction	Capsule enveloping the entire small intestine	Excision of the capsule	Thick vascular membrane proliferation. Fibrous dense and loose connective tissue; no active inflammatory granulation

TABLE 2. The case report of peritoneal encapsulation that is more likely to have been an abdominal cocoon.

	Age	Sex	Presentation	Findings	Operation
Sayfan et al ⁵	12	Female	Acute intestinal obstruction	Capsule encasing the terminal 30 cm of the ileum sparing the distal 10 cm of the ileum	Excision of the mass with end-to-end anastomosis

References

1. Foo KT, Ng KC, Rauff A, Foong WC. Unusual small intestinal obstruction in adolescent girls; the abdominal cocoon. *Br J Surg* 1978;65:427-30.
2. Siek JO, Cogwill R, Larkworthy W. Peritoneal encapsulation and abdominal cocoon: case reports and review of the literature. *Gastroenterology* 1983;84:1597-1601.
3. Rao PLNG, Mitra SK, Pathac IC. Abdominal cocoon: a cause of intestinal obstruction in a four-year-old girl. *Indian J Ped* 1979;XVI:11:1047-8.
4. Marinho A, Adelusi B. The abdominal cocoon: case report. *Br J Obstet Gynaecol* 1980;87:249-250.
5. Sayfan J, Adam Y, Reif R. Peritoneal encapsulation in childhood: case report, embryologic analysis and review of the literature. *Am J Surg* 1979;138:725-7.
6. Professor Cleland. On the abnormal arrangement of the peritoneum with remarks on the development of the mesocolon. *J Anatomy Physiology* 1868;11:201-6.
7. Huddy SPJ, Bailey ME. Small bowel obstruction due to peritoneal encapsulation. *Br J Surg* 1988;75:262.
8. Lickley JD, Cameron J. Note on a case of abnormal disposition of the peritoneum. *J Anatomy Physiology* 1907;41:88-90.
9. Papez JW. A rare intestinal anomaly of embryonic origin. *Anatomical Record* 1932;54:2:197-215.
10. Thorlakson PHT, Monie IW, Thorlakson TK. Anomalous peritoneal encapsulation of the small intestine: a report of three cases. *Br J Surg* 1953;40:490-3.
11. Lewin K, McCarthy LJ. Peritoneal encapsulation of the small intestine. *Gastroenterology* 1970;59:2:270-2.
12. Lee RG. Sclerosing peritonitis. *Dig Dis Sci* 1989;34(9):1473-6.
13. Windsor WO, Kurrein F, Dyer NH. Fibrinous peritonitis: a complication of proctolol therapy. *Br Med J* 1975;68.
14. Windsor WO, Griffiths DA, Davies CWO, Baddeley H. Sclerosing peritonitis due to proctolol: a report on 9 cases and their surgical management. *Br J Surg* 1977;64(4):229-35.
15. Brown P, Baddeley H, Read AE, Davies JD, McGarry J. Sclerosing peritonitis an unusual reaction to a B-adrenergic blocking drug (proctolol). *Lancet* 1974;1477-81.

HEPATIC CYSTADENOMA WITH MESENCHYMAL STROMA (CMS): REPORT OF CASE PRESENTING WITH OBSTRUCTIVE JAUNDICE

Mohamed B. Satti, MRCPath (Lond); Abdulaziz A. Al-Quorain, MD;
Majed S. Al-Awami, MD; Abdulla Y. El-Hassan, DMRD;
Ghassab Al-Ghassab, MD; Abdul Aziz Al-Jamaa, MBBS

In this communication we report the case of a 29-year-old female, who presented with progressive obstructive jaundice of 3 weeks duration. Oral hypoglycemic preparations were prescribed 3 months prior to presentation, because of a recent diagnosis of diabetes mellitus. Investigations including a computerized tomographic (CT) scan of the abdomen revealed a well demarcated intrahepatic cyst compressing the extrahepatic biliary tree at the porta hepatis. Surgical exploration disclosed a multilocular cyst in the medial aspect of the left lobe, which was aspirated and excised. Histopathological examination of the cyst wall, and a wedge of liver tissue, showed the lesion to be a rare biliary cystadenoma with mesenchymal stroma (CMS), causing large duct biliary obstruction. The patient improved rapidly, and was completely normal when last seen 6 months following the surgery.

The rarity of this newly categorized entity, combined with the unusual presentation—in a set up that might be confused with drug-induced jaundice—justify the reporting of this case.

Major causes of obstructive-type jaundice include some forms of hepatitis due to microbiologic agent, drugs [1] and large duct organic obstruction. Large duct organic obstruction is commonly the result of a stone, a stricture (benign or malignant), or an external compression by space-occupying lesions, including cysts and neoplasms. The entity of biliary cystadenoma, though previously recognized by Bevan [2] as

early as 1919, was only recently sufficiently categorized by Wheeler and Edmondson [3]. Based on distinctive histological and clinical characteristics, Wheeler and Edmondson renamed a subgroup of these lesions as "Cystadenoma with Mesenchymal Stroma (CMS)." They found that such lesions occurred exclusively in young and middle aged females, who commonly presented with abdominal discomfort, with or without an associated mass. Jaundice, as a presenting symptom, was rare [3,4]. We report a typical case of CMS, presenting with obstructive jaundice in a diabetic who was on oral hypoglycemic agents.

Case Report

A 29-year-old female was admitted to the hospital with the chief complaint of a 3 week history of itching and yellowish discoloration of the sclera. She had nausea, but no vomiting; her urine was dark yellow, and her stools were pale in color. There was no history of blood transfusion, contact with a jaundiced patient, alcohol abuse or drug abuse. However, 4 months prior to admission, she was discovered to be diabetic, and was put on oral hypoglycemic Tolazamide 250 mg daily which she used for 3 weeks. This drug was changed to minidiab tablet (glipizide 5 mg daily) because of the onset of pruritus. She continued on minidiab for 3 months, until a week prior to admission, when she was shifted to insulin. Nevertheless, pruritus persisted. Her past medical history indicated she had primary infertility for the last 12 years. She received a course of primolut N (Norethisterone) for 3 months, a year prior to presentation. Her family history indicated both her parents and one sister were diabetic.

From the Department of Pathology (Dr. Satti), King Fahd Hospital of the University, Al-Khobar.

Address reprint requests and correspondence to Dr. Satti: King Fahd Hospital of the University, P.O. Box 40029, Al-Khobar 31952, Saudi Arabia.

Accepted for publication 13 August 1990.

On examination she was a well-built female, deeply jaundiced, not pale, cyanosed or febrile. Her vital signs were stable, blood pressure was 120/80 mm Hg, and she had no stigmata of chronic liver disease. The skin showed scratch marks, but no bruises. The cardiopulmonary system was unremarkable. Abdominal examination revealed no hepatomegaly, splenomegaly or ascites. Other systems, including pelvic organs, were unremarkable.

Routine testing on admission resulted in the following. Urinalysis showed bilirubin +++ but no urobilinogen or sugar. Complete blood count (CBC) showed a hemoglobin of 12.3 gm/dl, WBC $4.4 \times 10^9/L$, platelets $320 \times 10^9/L$ and reticulocyte count 0.5%. The Coomb's test was negative. All serologic tests including those for hepatitis B viral infection were negative. Liver function tests (LFT) were as shown in Table 1. Imaging procedures included an abdominal ultrasound that showed a liver of normal size, but with a 7.8×6.8 cm complex area in gallbladder fossa. CT scan of the abdomen, with contrast enhancement, showed a very well demarcated lobulated cystic lesion in the anterior part of the left lobe of liver, compressing over the porta hepatis region (Figure 1). Serology for hydatid disease obtained was negative. As the findings were not completely conclusive to explain the nature of the cyst, exploratory surgery was decided upon. At

laparotomy, a large solitary multilocular cyst $7 \times 6 \times 5$ cm was found in the medial segment of the left lobe of the liver compressing the common hepatic duct at the porta hepatis. Aspiration revealed 500 cc of straw colored mucinous fluid. Cystostomy and Roux-en-Y cystojejunostomy were performed, and a wedge of liver tissue was taken. An intraoperative cholangiogram showed patency of the biliary tree.

Pathological Examination

The material submitted showed several gray-white membranous fragments of tissue. The largest measured $8 \times 2 \times 0.4$ cm. Also, a wedge of greenish liver tissue $1 \times 0.8 \times 0.5$ cm was received. Histological examination of the wall of the cyst showed an epithelial lining formed of columnar non-ciliated mucin secreting cells, overlying a cellular fibrous stroma (Figure 2). The latter consisted of spindle shaped fibroblasts, in the outermost part in which a thick layer of collagen fibers was present. The stroma had a striking resemblance to ovarian stroma. No atypia of the epithelium, or invasion of the stroma, was noted. The diagnosis was biliary cystadenoma, with mesenchymal stroma. The wedge of liver tissue showed preserved architecture. Marked canalicular cholestasis was noted, in addition to widening of the portal tracts due to edema, and infiltration by inflammatory cells, mostly neutrophils (Figure 3). Marginal duct proliferation was a notable feature in the portal triads (Figure 4). No liver cell

TABLE 1. Liver function tests (LFT).

Date	Bili (T)	Bili (D)	SGOT	SGPT	GGTP	ALP	LDH
On admission	7.7	6.7	179	181	375	66	148
Pre-op Day							
2 W later	16.8	14.0	118	110	314	54	146
P-op Day	8.7	6.8	100	94	280	44	119
1 W P-op	4.2	3	61	35	180	22	114
3 W P-op	1.1	0.3	35	28	80	13	144
6 M P-op	0.8	0.2	27	32	70	12	110
Normal values	0.1	<0.4	7-41	5-35	5-85	5-14	100-
	1.5	mg/dl	IU/L	IU/L	IU/L	IU/L	190
	mg/dl						IU/L

Pre-op = Preoperative; P-op = postoperative; W = weeks; M = months; T = total; D = direct; Bili = bilirubin; SGOT = serum glutamic oxalocetic transaminase; SGPT = serum glutamic pyruvic transaminase; GGTP = gamma-glutamyl transpeptidase; ALP = alkaline phosphatase; LDH = lactic dehydrogenase.

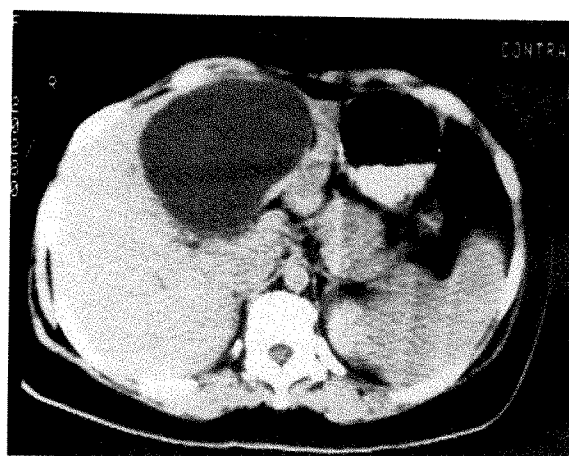


FIGURE 1. Computed tomographic scan of the liver after administration of contrast material, demonstrates presence of a single cystic lesion in the medial part of the left lobe.

necrosis, eosinophils, or evidence of hepatitis was noted. The features were those of large duct organic obstruction.

Follow-up

The patient had an uneventful postoperative recovery. Follow-up examination revealed progressive improvement in the jaundice and liver function tests (Table 1). The patient was completely normal when last seen 6 months postoperatively, with a fasting blood sugar of 112 mg/dl. She was under dietary control for her diabetes.

Discussion

CMS of the liver and bile ducts was characterized by Wheeler and Edmondson [3] as a lesion that occurred exclusively in females. It showed the distinctive histologic characteristics of a cyst lining of columnar to cuboidal, non-ciliated, mucin secreting epithelium, overlying a cellular stroma resembling primitive mesenchyma and sur-

rounded by an outer collagenous layer. The hepatic lesion from our patient demonstrated these typical histologic features (Figure 2). These same features were previously described by Ishak [4] in 7 of their 8 female patients with biliary cystadenoma, and in the one case reported in the case records of the Massachusetts General Hospital in 1985 [5]. The lesion from our patient had a multilocular gross pattern similar to all previously reported cases [3-5].

The exact incidence of CMS is unknown. Ishak [4] stated that the cystadenomas make up only 4.6% of the total number of reported intrahepatic cysts of bile duct origin, and 80% occurred in females. However, Wheeler and Edmondson [3] reviewed most of the 67 cases of cystadenomas reported, and found that of 34 well described cases only 27 (79%) met the diagnostic criteria of CMS. All 27 were females with a mean age of 44.1 years, correlating closely with the parameters of their 13 cases (all females mean age 41.7 years). In this review, Edmondson and Wheeler [3] found

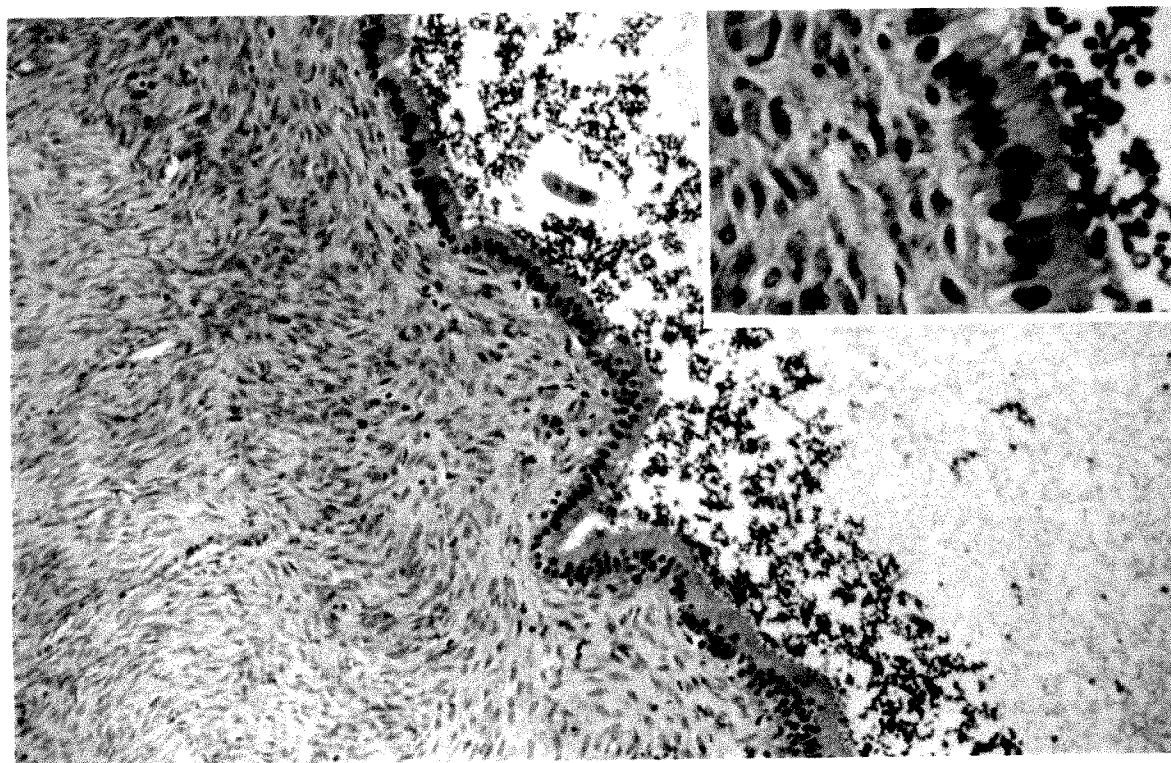


FIGURE 2. Wall of cyst lined by non-ciliated columnar epithelium overlying a densely cellular mesenchymal stroma. (Hematoxylin-eosin stain; original magnification, $\times 125$.) Inset: non-ciliated columnar mucin secreting epithelium. (Hematoxylin-eosin stain; original magnification, $\times 325$.)

that cystadenomas, without the typical dense cellular stroma, had a higher mean age (53.4 years), and no female predominance.

Our patient presented with gross obstructive jaundice with no abdominal pain or mass felt. Both, or either, of the latter two features occurred in 12 out of 13 cases of CMS in the series of Edmondson and Wheeler [3]. Only two patients from the latter series had had obstructive jaundice. One out of 8 patients reported by Ishak [4] presented with obstructive jaundice. The cause of the obstruction in all 4 patients, including ours, was due to external compression of the biliary tree by the neoplasm.

Pruritus, followed by jaundice, developed in our patient 3 weeks after being started on the oral hypoglycemic Tolazamide, a drug that may produce a cholestatic type of jaundice [1]. Van-Thiel [6] reported on a 62-year-old male diabetic who developed jaundice within a month of starting Tolazamide. His liver biopsy showed marked centrilobular hepatocellular necrosis and cholestasis. However, in our case, drug jaundice was excluded by the operative finding of external compression

of the common hepatic duct, and by the definite histologic features of a large duct organic obstruction on liver biopsy (Figures 3,4). Furthermore, following relief of the obstruction, the patient showed a remarkable progressive improvement of her LFT, particularly bilirubin levels which dropped from 16.8 mg/dl on the preoperative day to 1.1 mg/dl 3 weeks later. Similarly, GGTP, known to be elevated in cases of biliary obstruction [7,8], dropped from a level of 375 IU/L on admission to a normal of 80 IU/L, 3 weeks postoperatively (Table 1).

The differential diagnosis of solitary cystic lesions in the liver included congenital solitary, or simple cysts [9]. These are generally unilocular, contain a serous or bile-stained fluid and are lined by cuboidal epithelium. Of the acquired solitary cystic lesions, hydatid disease [10], abscess formation and cystic degeneration in malignant neoplasms [11] deserve to be mentioned. Serology for hydatid disease in our case was negative.

Wheeler and Edmondson [3] considered CMS as premalignant tumors and recommended total excision, whenever feasible, with adequate surgi-

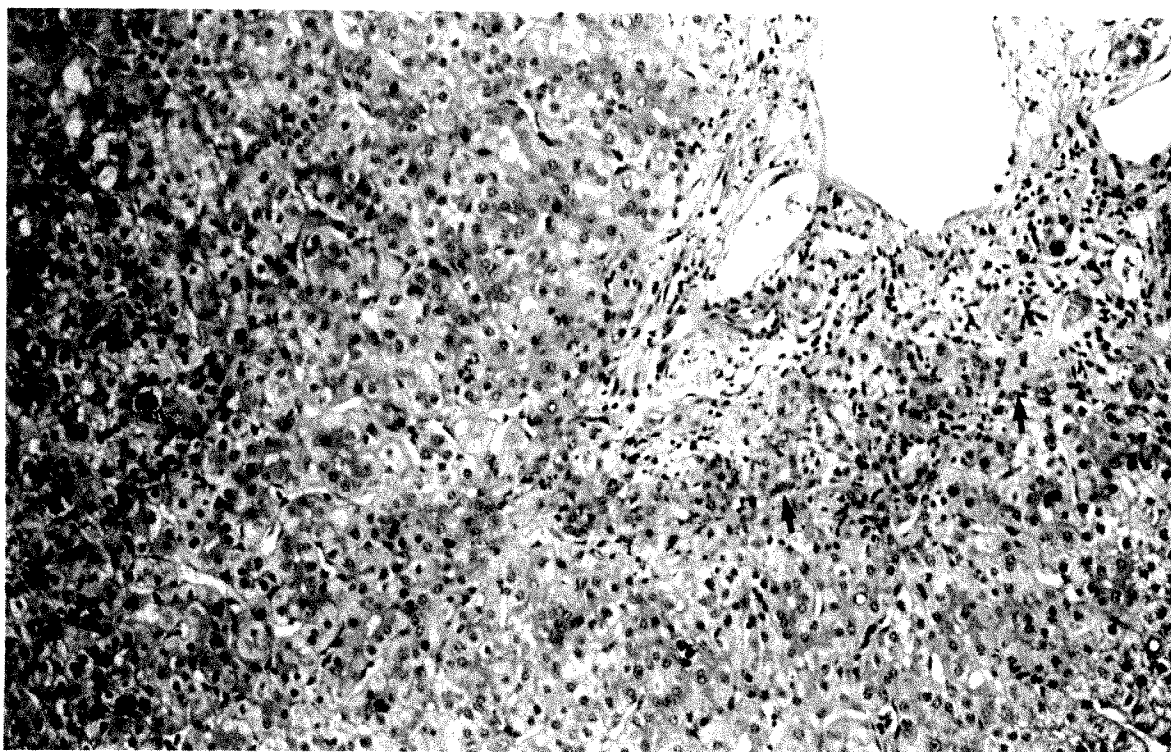


FIGURE 3. Wedge of liver tissue: edematous portal tract (upper right corner), infiltrated by inflammatory cells and showing marginal duct proliferation (arrows). Lobular cholestasis noted (arrow head). (Hematoxylin-eosin stain; original magnification, $\times 125$.)

cal margins. Four of their cases with the typical mesenchymal stroma showed malignant change of the epithelium. All four were females, with a sex ratio different from that of the six patients with cystadenocarcinoma reported by Ishak [4], with a M:F = 2:1. Malignant transformation of a previously diagnosed biliary cystadenoma was reported by Woods [12], in a patient who had 3 recurrences over a 6-year period. Although histological examination of the CMS in our patient did not reveal any features of epithelial atypia or stromal invasion, long term follow-up would be recommended, as total excision was not performed.

The histogenesis of CMS is controversial. Due to the histologic resemblance of CMS to embryonic gallbladder and large bile ducts, derivatives of the foregut, it was suggested that CMS originates from ectopic rests of this primitive tissue [3]. Lesions of histology similar to CMS were described in the pancreas [13]. Recently an intrahepatic biliary cystadenoma, with increased level of tissue estrogen receptor content, was reported in a patient who was on oral contraceptives for one year [14].

In conclusion, we reported a typical case of hepatic CMS presenting with obstructive jaundice, a rare clinical manifestation of this entity. The patient improved dramatically following excision of the lesion. Since total excision was not performed, and recognizing the malignant potential of this neoplasm, long-term follow up was recommended.

References

1. Zimmerman HJ, Maddrey WC. Toxic and drug-induced hepatitis. In: Schiff L, Schiff ER, eds. *Diseases of the liver*, ed 5. Philadelphia: Lippencott, 1982;621:92.
2. Bevan AD. Multilocular cystadenoma of the liver. *Surg Clin Chicago* 1919;3:887-92.
3. Wheeler DA, Edmondson HA. Cystadenoma with mesenchymal stroma (CMS) in the liver and bile ducts: a clinicopathologic study of 17 cases, 4 with malignant change. *Cancer* 1985;56:1434-45.
4. Ishak KG, Willis GW, Cummins SD, Bullock AA. Biliary cystadenoma and cystadenocarcinoma: report of 14 cases and review of the literature. *Cancer* 1977;38:322-38.
5. Case records of the Massachusetts General Hospital (Case 46-1985). *N Engl J Med* 1985;313:1275-82.
6. Van-Thiel DH, De Belle R, Mellow R, et al. Tolazamide hepatotoxicity: a case report. *Gastroenterology* 1974;67:506-10.

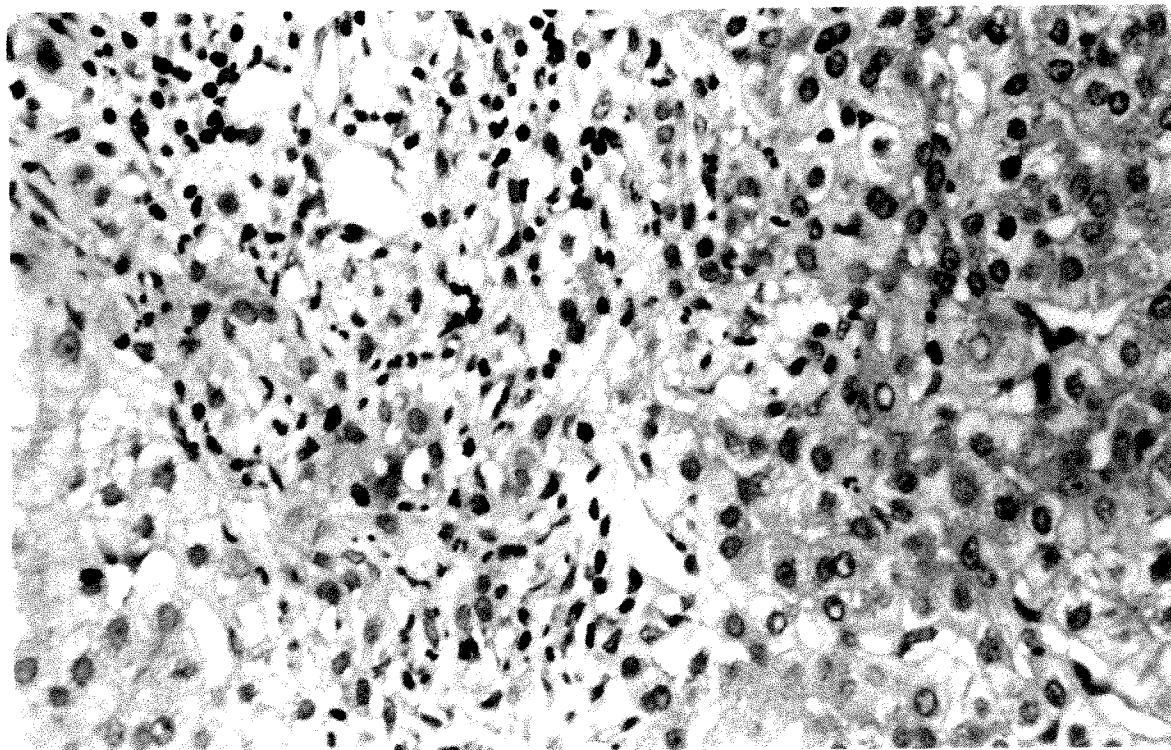


FIGURE 4. Portal tract showing edema, neutrophil polymorphs and marginal duct proliferation. (Hematoxylin-eosin stain; original magnification, $\times 325$.)

7. Zein M, Discombe G. Serum gamma-glutamyl transpeptidase as a diagnostic aid. *Lancet* 1970;10:748-50.
8. Ravel R. Liver and biliary tract tests. In: Ravel R, ed. *Clinical Laboratory Medicine*, ed 4. Chicago. Year Book Medical Publishers, 1984;211-26.
9. Longmire WP Jr, Mandiola SA, Gordon HE. Congenital cystic disease of the liver and biliary system. *Ann Surg* 1971;174:711-26.
10. Langer JC, Rose DB, Keystone JS, Taylor BR, Langer B. Diagnosis and management of hydatid disease of the liver: a 15-year North American experience. *Ann Surg* 1984;199:412-7.
11. Dent GA, Feldman JM. Pseudocystic liver metastases in patients with carcinoid tumors: report of three cases. *Am J Clin Pathol* 1984;82:275-9.
12. Woods GL. Biliary cystadenoma: case report of hepatic malignancy originating in benign cystadenoma. *Cancer* 1981;47:2936-40.
13. Hodgkinson DJ, ReMine WH, Weiland LH. Pancreatic cystadenoma: a clinicopathologic study of 45 cases. *Arch Surg* 1978;113:512-9.
14. Suyama Y, Horie Y, Suou T, et al. Oral contraceptives and intrahepatic biliary cystadenoma having an increased level of estrogen receptor. *Hepatogastroenterol* 1988;35:171-4.

THE BUDD-CHIARI SYNDROME: A CASE REPORT AND REVIEW OF CURRENT MANAGEMENT OPTIONS

Mohamed A. Al-Karawi, Fachartz(W. Germany);
Abdul M. Ahmed, MBBS, MRCP(UK);
Abdel Rahman El-Shiekh Mohamed, DipVen, MRCP, DTM&H

A 33-year-old Saudi housewife presented with a six-week history of upper abdominal pain of sudden onset, progressive abdominal distention, and edema of the legs accompanied by mild jaundice.

She was on no medications at the time of presentation, but on direct questioning she admitted to taking oral contraceptives in the past (some 10 years ago), when she took them for four years. It was also possible that she might have taken some local herbs, but we were unable to identify their nature. The rest of the history, however, was unremarkable.

Physical examination showed an ill-looking young woman who was jaundiced and pyrexial, but mentally alert. Abdominal examination showed moderate ascites with hepatomegaly, but the spleen was not palpable. There was bilateral leg edema up to mid thighs. The rest of the examination was noncontributory.

Initial laboratory tests revealed grossly abnormal liver function test results, with markedly elevated total bilirubin and liver enzymes. Serum albumin was low. Full blood count was normal, but the prothrombin time was prolonged (more than twice the control).

Other relevant blood tests were normal, and those included viral hepatitis screen for Type A and Type B, blood film for malaria parasites, autoantibody profile and serology titers for amoeba, brucella, schistosoma and hydatid disease.

Abdominal ultrasound scan confirmed the pres-

ence of hepatomegaly and ascites, with evidence of splenic enlargement. The liver appearance was nonspecific.

Gastroscopy examination showed two non-bleeding grade II esophageal varices.

She was kept under observation and on conservative management, pending performing a liver biopsy. Her condition continued to deteriorate rapidly and she became grossly encephalopathic. She was referred to this hospital for further evaluation at that time.

A repeat abdominal ultrasound scan, on the day of arrival to this hospital, showed that the liver was markedly enlarged with enlargement of the caudate lobe. This appeared to be compressing the inferior vena cava.

The hepatic veins were very poorly seen, with no visualization of the right hepatic vein. The middle and left hepatic veins appeared patent, and the spleen was slightly enlarged.

Liver computed tomography (CT) and magnetic resonance imaging (MRI) scans further confirmed these findings, and the MRI in particular showed the hepatic veins to be largely occluded.

The patient's condition up to this stage remained somewhat stable, and with extreme care a liver biopsy was performed. This showed evidence of hemorrhagic necrosis with lobular collapse. Portal venous radicles were distended, and there was partial or complete occlusion of central veins by fibrointimal proliferation.

The possibility of Budd-Chiari syndrome was considered; therefore, a venocavogram was carried out. This study showed tapering of the inferior vena cava at the site of the caudate lobe of the liver but otherwise the cava was patent. The right hepatic vein was occluded. The intravenous pressure measurements were not taken.

From the Gastroenterology Division, Department of Medicine; Riyadh Armed Forces Hospital, Riyadh, Saudi Arabia.

Address reprint requests and correspondence to Dr. Ahmed: (W956), Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia.

Accepted for publication 13 October 1990.

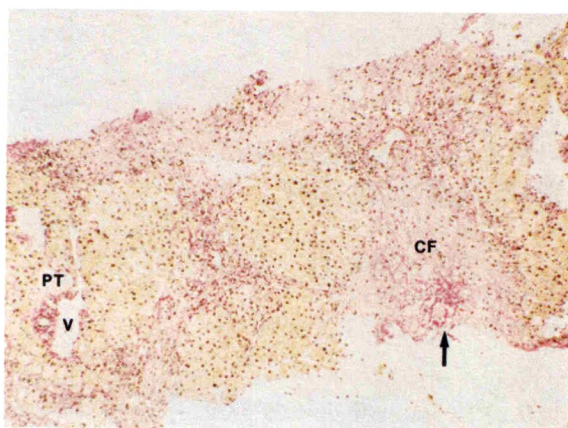


FIGURE 1. Liver showing bridging central folds (CF) and pattern of reverse lobulation with intact parenchyma surrounding a normal portal tract (PT). Note that the portal venous radical is dilated (V). An occluded central vein is present in one of the areas of fibrosis (arrow) as well as several newly formed by-pass channels (arrowheads). (van Gieson stain.)

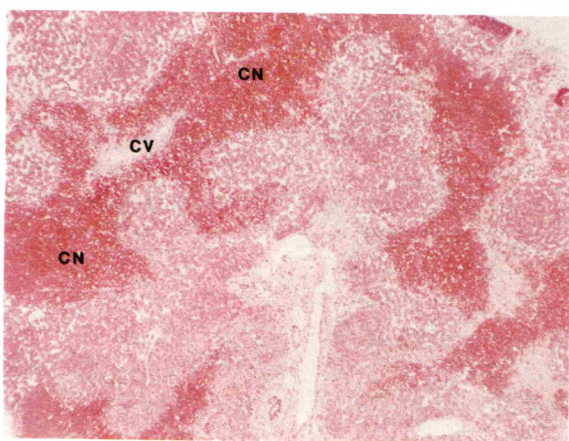


FIGURE 2. Hemorrhagic centrilobular necrosis (CN) surrounds normal periportal parenchyma. A small central vein (CV) with fibrous thickening of its wall is seen in the necrotic zone. The portal tract (lower center) shows dilation of portal venous radicals but is otherwise normal. (Hematoxylin-eosin stain.)

The patient continued to deteriorate despite intensive therapy with diuretics, vitamin K, low salt/high calorie diet, and salt-poor albumin infusions. She was variably encephalopathic; her liver function did not improve; and she became progressively more edematous.

The option of surgical treatment was considered and at the end of the third week in the hospital an insertion of a mesocaval shunt was successfully performed. A postoperative angiographic study revealed a patent shunt. The operation was fol-

lowed by dramatic improvement; the patient was less drowsy, eventually fully alert, she lost most of the retained fluid, and liver chemistry returned to near normal two weeks postoperatively.

The patient was eventually discharged home, and followed-up satisfactorily for six months. She was then readmitted to this hospital for a follow-up liver biopsy, and to check the patency of the mesocaval shunt. This proved patent on a study of selective augmented superior mesenteric arteriogram with late venous phase. Histology from liver biopsy (Figure 1) showed complete disruption of the lobular central vein surrounded by fibrous tissue representing centrilobular areas of hemorrhagic necrosis which was seen in the previous biopsy (Figure 2). In addition, bands of fibrous tissue were seen linking the portal areas. The final histological diagnosis was bridging fibrosis.

Discussion

Following the initial reports of Budd in 1845 and Chiari in 1899 on the occurrence of hepatic vein occlusion, a number of reports have appeared on the genesis of this syndrome [1]. The etiological factors include: use of oral contraceptives, pregnancy, underlying malignancy, cytotoxic chemotherapy, herbal tea and herbal medicines, congenital webs in the inferior vena cava and/or hepatic veins, abdominal trauma and thrombotic events [1-8]. An association with ulcerative colitis [9], and with lupus anticoagulant, has also been described [10]. Recently Young et al [11] reported a case of idiopathic granulomatous venulitis, a rare type of vasculitis affecting tiny liver veins, causing a type of Budd-Chiari syndrome, which is reversible with prednisolone.

In a large number of cases, however, the cause remains unknown. In a series of 164 cases the etiology was either unidentified or inadequately established in 70.1% [1]. In another series, some ten years later, the figure dropped to 25% [4]. This was presumably due to advances in investigative technology.

In our patient, the two most relevant etiological factors are the possible use of herbal medicines, and exposure to oral contraceptives. The mechanism of causation of the syndrome by oral contraceptives remains unclear, and the time span between the use of oral contraceptives and diag-

nosis of Budd-Chiari syndrome varies considerably, ranging from two-weeks up to five years [1]. It is the recent use as opposed to the past use of oral contraceptives that is commonly related to the causation of the disease. We are, therefore, not certain whether the past use of the pill in this patient is a factor. However, if it is a factor, then our patient would be the first reported case where the syndrome has developed following such a long period of cessation of oral contraceptives.

Hepatic veno-occlusive disease of the liver, regarded by some as a variant of Budd-Chiari syndrome, has been increasingly reported in areas of the Middle East, Far East, Asia, and Central America in association with the use of herbal tea and herbal medicines [15-16]. Pyrrolizidine alkaloids are incriminated in the majority of cases [7,15,16]. Although we have been unable to quantify those substances to any extent in this patient, the possibility of their use could not be completely eliminated.

Clinically, Budd-Chiari syndrome is characterized by abdominal pain, hepatomegaly and ascites [1]. The course of the disease, and the outcome in a given patient, is difficult to predict [17] and the natural history is still uncertain [18]. The fact remains that the prognosis is dismal if the disease is left untreated. In the series of Tavill et al, six out of nineteen patients died within the first year and seventeen were dead after three and a half years.

A retrospective review by McCarthy et al [19] of thirty patients with documented Budd-Chiari syndrome disclosed an overall mortality of 57%. Medical treatment alone was associated with 86% mortality; hepatic failure was the most common cause of death.

The most widely applied surgical treatment for Budd-Chiari syndrome at present is portosystemic shunting, the site of the shunt is largely determined by the level of occlusion. For those with inferior vena cava obstruction and/or high IVC, pressure shunts to the right of the atrium have been advocated [18]. However, shunts like these do not last longer because of their length. When the IVC is patent, then a portocaval or preferably mesocaval shunt would be more appropriate [17-24]. The latter is preferred partly because of the ease of construction, and partly because of the lower incidence of perioperative and postopera-

tive complications. Drapanas et al [23] studied 80 cases with interposition mesocaval shunts and concluded that the shunt can be readily performed, carries a low operative mortality, and a low incidence of encephalopathy; and it can be applied to most patients with portal hypertension. Cumulative life survival tables indicated an overall 75% five year survival in the entire group. A portal to systemic venous shunt, utilizing a dacron graft anastomosed to the superior mesenteric vein, can be expected to stay open in over 90% of patients [24].

Experience with side-to-side portocaval shunts has shown this to be a reliable and effective procedure also, and survival of up to 5 years has been reported [17,21].

Other options of management are orthotopic liver transplant and, more recently, the percutaneous transluminal angioplasty with or without laser therapy. Laser therapy is reliable for use in percutaneous transluminal angioplasty (PTA) for treatment of hepatic inferior vena cava obstruction, as it is in treatment of arteriosclerosis [25]. It will become more widely used with improvements in the laser delivery system. PTA alone has proved a safe and effective mode of therapy also in membranous obstruction of IVC and/or the hepatic veins, and it is hoped that it will be equally successful in the non-membranous type of obstruction [27]. It is not clear at this early phase of this modern therapy whether it will have to be repeated on several occasions, in view of the possibility of high reocclusion rate.

Finally, of the surgical measures employed so far, orthotopic liver transplantation is the only curative procedure for this condition and this is best performed early in the clinical course of the illness [13,15].

Our patient will be considered for liver transplant should her shunt reocclude and her symptoms recur. A major complication of these shunts, despite their high success rate, is that they are considered by some authorities as a relative contraindication to transplant operation because of technical difficulties [19].

The hope of the future lies in the improvements of techniques of PTA and laser therapy, but failure to achieve this will leave us to face the ever demanding option of liver transplant—an issue which at present is receiving a lot of attention.

Acknowledgment

We would like to thank Prof. E. C. Sweeney from the histopathology department for reviewing the histopathology figures and for his valuable comments on this paper.

References

- Hoyuma AM, Schiff L, Helfman EL. Budd-Chiari syndrome in women taking oral contraceptives. *Am J Med* 1971;50:137-9.
- LaLone G, Theoret G, Daloze P, et al. Inferior vena cava stenosis and Budd-Chiari syndrome in a woman taking oral contraceptives. *Gastroenterol* 1982;82:1452-6.
- Valla D, Le MG, Poynard T, et al. Risk of hepatic vein thrombosis in relation to recent use of oral contraceptives. *Gastroenterol* 1986;90:807-11.
- Powel-Jackson PR, Melia W, Canalese J, et al. Budd-Chiari syndrome: clinical patterns and therapy. *Quart J Med* 1982;201:78-82.
- Anonymous. Hepatic outflow obstruction. *Lancet* 1985;2:310-11.
- Ridker PM, McDermott WV. Comfrey herb tea and hepatic veno-occlusive disease. *Lancet* 1989;1:657-8.
- Ridker PM, Ohkuma S, McDermott WV, et al. Hepatic veno-occlusive disease associated with the consumption of pyrrolizidine containing dietary supplements. *Gastroenterol* 1985;88:1050-4.
- Khuroo MS, Datta DV. Budd-Chiari syndrome following pregnancy: report of 16 cases with roentgenologic, hemodynamic and histologic studies of the hepatic outflow tract. *Am J Med* 1980;68:113-21.
- Chesner IM, Muller S, Newman J. Ulcerative colitis complicated by Budd-Chiari syndrome. *Gut* 1986;27:1096-100.
- Pomeroy C, Knodell RG, Swanin WR, et al. Budd-Chiari syndrome in a patient with lupus anticoagulant. *Gastroenterol* 1984;86:158-61.
- Young ID, Clark RN, Malney PN, et al. Response to steroids in Budd-Chiari syndrome caused by idiopathic granulomatous venulitis. *Gastroenterol* 1988;94:503-7.
- Putmen CW, Porter KA, Weil R, et al. Liver transplantation for Budd-Chiari syndrome. *JAMA* 1976;236:1142-3.
- McDougall BRD, McMaster P, Calne RY, Williams R. Survival and rehabilitation after orthotopic liver transplantation. *Lancet* 1980; .
- Starzl TE, Koep L, Porter KA, et al. Decline in survival after liver transplantation. *Lancet* 1980; .
- Kumana CR, Ng M, Lin HJ, et al. Herbal tea induced hepatic veno-occlusive disease: quantification of toxic alkaloid exposure in adults. *Gut* 1985;26:101-4.
- Mohabbat O, Srivastava RN, Younos MS, et al. An outbreak of hepatic veno-occlusive disease in North Western Afghanistan. *Lancet* 1976;2:269-71.
- Schramek A, Better OS, Brook JG, et al. New observations in the Budd-Chiari syndrome. *Ann Surg* 1974;180:368-72.
- Vons C, Boursstyn E, Bonnet P, et al. Results of portal systemic shunts in Budd-Chiari syndrome. *Ann Surg* 1986;203:366-70.
- McCarthy PM, Van Heerden JA, Adson MA, et al. The Budd-Chiari syndrome: medical and surgical management of 30 patients. *Arch Surg* 1985;120(6):657-62.
- Noble MJA. Hepatic vein thrombosis complicating polycythemia vera. *Arch Intern Med* 1967;120:105-8.
- Pezzuoli G, Spina GP, Opecher E, et al. Portacaval shunt in the treatment of primary Budd-Chiari syndrome. *Surgery* 1985;98(2):319-23.
- Hugnet C, Deliere T, Oliver JM, Levy VG. Budd-Chiari syndrome with thrombosis of the inferior vena cava: long term patency of mesocaval and cavoarterial prosthetic bypass. *Surgery* 1984;95:108-11.
- Drapana T, Lo Cicero J, Dowling JB. Hemodynamics of the interposition mesocaval shunt. *Ann Surg* 1978;181:523-31.
- Cameron JL, Maddrey WC. Mesoatrial shunt: a new treatment for Budd-Chiari syndrome. *Ann Surg* 1978;187:402.
- Furui S, Yammanchi T, Ohtomo K, et al. Hepatic inferior vena cava obstruction: clinical results of treatment with percutaneous transluminal laser assisted angioplasty. *Radiology* 1988;166(3):673-7.
- Hosie KB, Bolia A, Watkin DFL. Treatment of Budd-Chiari syndrome by percutaneous transluminal angioplasty. 1988;2:158-9.
- Sparno J, Chang J, Trasi S, Bonnano C. Treatment of the Budd-Chiari syndrome with percutaneous transluminal angioplasty: case report and review of literature. *Am J Med* 1987;82(4):821-8.

HEREDITARY PYROPOIKILOCYTOSIS: A CASE REPORT WITH THERMAL STUDIES AND SCANNING ELECTRON MICROSCOPY

Salim H. Khalil, MD; Randa M. Nounou, MD

Hereditary pyropoikilocytosis (HPP) is a severe, relatively rare, congenital (autosomal recessive) hemolytic anemia, characterized by strikingly abnormal red cell morphology (microspherocytosis, aniso-poikilocytosis, schistocytosis and a moderate degree of elliptocytosis) and a lowered thermal threshold for heat-induced red cell fragmentation and lysis [1,2]. Heat-treated erythrocytes of such patients undergo fragmentation and show membrane budding at 45°C, whereas normal red blood cells require exposure to 49°C or above to show the same morphology [3].

Considerable evidence indicates that the assembly of the red cell skeleton is abnormal in such patients as a result of one or more inherited defects in the spectrin molecule [4,5].

The condition has been reported in American black children, and the first two occurrences in Saudi children were reported from Dhahran Health Centre [6]. We report another Saudi patient with thermal studies (using several controls) and scanning electron microscopy.

Case Report

A 29-year-old Saudi pregnant female was referred to King Faisal Specialist Hospital and Research Centre at the 31st week of gestation, with the diagnosis of severe hydrops fetalis and past history of neonatal deaths and stillborn. The blood of both the patient and her husband was morphologically normal, and they have no history of hemolytic anemia. The mother's serum anti-

bodies for Rh isoimmunization were negative. Hematological findings of the fetal blood are shown in Table 1. Hemoglobin electrophoresis by cellulose acetate membrane has shown 100% fetal hemoglobin, which is consistent with the patient's age. The peripheral blood morphology suggested the possibility of HPP.

Figure 1A shows hypochromia, microcytosis, target cells, microspherocytes, fragmented forms, along with a few nucleated red blood cells.

Figure 1B shows the patient's blood post heat treatment at 45°C for 15 minutes.

Three days later the baby's condition deteriorated and she expired. Labor was induced, and postmortem examination showed a female fetus without external congenital anomalies, but with severe hydrops, focal subintimal deposition of calcium in all major and medium size arteries, coarctation of the aorta with aneurysmal dilatation of the ascending part of the aorta, and compensatory hypertrophy of the heart. There was no evidence of erythroblastosis fetalis. A diagnosis of calcinosis fetalis was made. This baby is known to have two healthy siblings, but no studies were done on them, because of their absence from Riyadh.

Discussion

The bizarre morphological changes of red blood cells of our patient resemble those described by

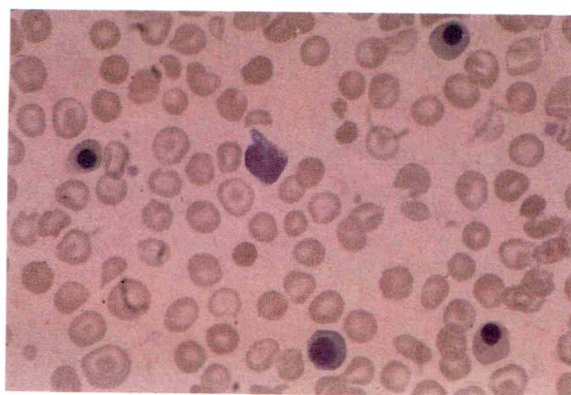
TABLE 1. Hematological findings.

WBC	5.0 × 10 ⁹ /L
HGB	110 g/L
RBC	2.8 × 10 ⁹ /L
HCT	0.327
MCV	117.2 fl
MCHC	393 g/L
PLT	110 × 10 ⁹ /L
Reticulocyte count	212 × 10 ⁹ /L
Hb-H	Negative
NRBC's	4/100 WBC

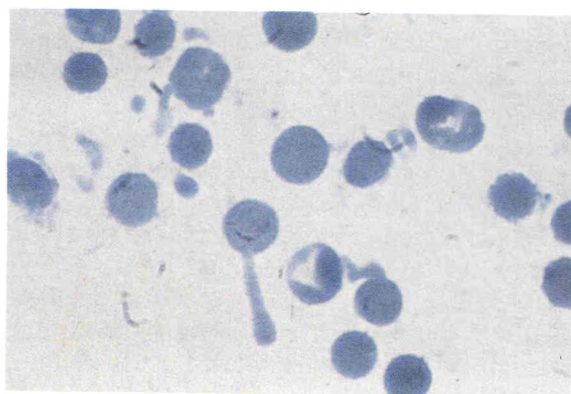
From the Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh.

Address reprint requests and correspondence to Dr. Khalil: Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

Accepted for publication 5 November 1990.



A



B

FIGURE 1. (A) Patient peripheral blood. (B) Patient peripheral blood at 45°C for 15 minutes.

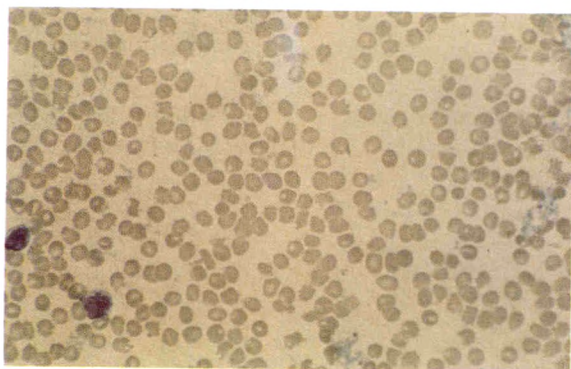
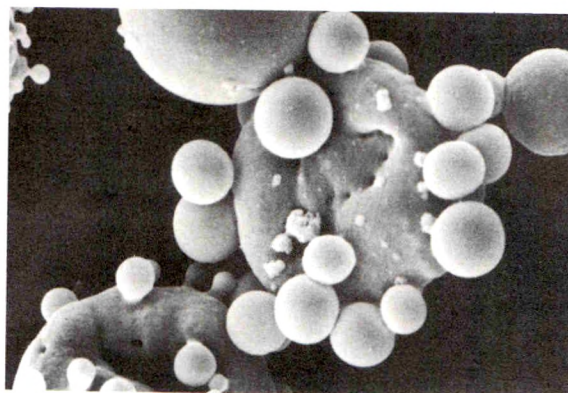


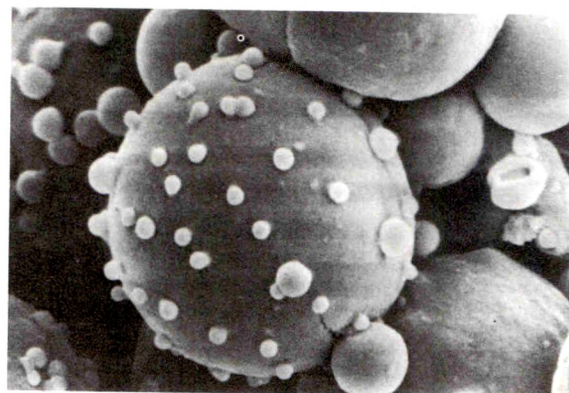
FIGURE 2. Peripheral blood of normal control heated at 45°C for 15 minutes.

Zarkowsky in 1973 and 1975, and also those of two Saudi cases reported from Dhahran Health Centre as HPP.

In this report, our thermal studies included as controls, a normal Saudi blood donor, a case of hereditary elliptocytosis (HE), and a case of hereditary spherocytosis (HS) heated in a water bath at 45°C for 15 minutes.



A



B

FIGURE 3. (A) Scanning electronmicrographs of patient's RBC's showing membrane. (B) Budding formation of microspherocytes post-heat treatment at 45°C for 15 minutes.

Figure 2 shows that red blood cells of the normal donor did not demonstrate membrane budding or formation of microspherocytes following heat treatment at 45°C, but they could be demonstrated after exposure to higher temperature of 49°C. Figures 3A and 3B show the scanning electron micrographs of the blood of our patient post heat treatment at 45°C for 15 minutes. The red blood cells demonstrate elaborate membrane budding.

The morphologic abnormalities of the red blood cells noted in this patient and the increased thermal sensitivity of his erythrocytes are characteristic of HPP.

To confirm the diagnosis of HPP, SDS-PAGE (sodium dodecyl sulfate-polyacrylamide electrophoresis) is required to demonstrate reduction or lack of alpha I-T80 peptide (domain) of the spectrin molecule [7,8]. Unfortunately, this technique is not available in our laboratory.

Acknowledgment

The authors would like to thank Dr. Geoffrey M. Brittin for his critical review of this manuscript and Mr. Mohammed Bakry for his assistance in scanning electron microscopy.

References

1. Zarkowsky HS, et al. A congenital haemolytic anemia with thermal sensitivity of the erythrocyte membrane. *Br J Haematology* 1975;29:537-43.
2. Coetzer TL, Palek J. Partial spectrin deficiency in hereditary pyropoikilocytosis. *Blood* 1986;67(4):919-24.
3. MacDougall L, Moodley G, Quirk M. The pyropoikilocytosis-elliptocytosis syndrome in a black South African infant: clinical and hematological feature. *Am J Hematology/Oncology* Fall 1982;344-8.
4. Lawler J, Liu SC, Palek J, et al. Molecular defects of spectrin in hereditary pyropoikilocytosis. *J Clin Invest* 1982;70:1019-30.
5. Lawler J, et al. Molecular heterogeneity of hereditary pyropoikilocytosis: identification of a second variant of the spectrin alpha sub-unit. *Blood* 1983;62(5):1182-9.
6. Mallouh A, Sa'di AR, Ahmad MS, et al. Hereditary pyropoikilocytosis: Report of two cases from Saudi Arabia. *Am J Med Genetics* 1984;18:413-7.
7. Palek J, Liu SC, Liu PY, et al. Altered assembly of spectrin in red cell membrane in hereditary pyropoikilocytosis. *Blood* 1981;57:130-9.
8. Gutati GL, Hyun BH. Hereditary pyropoikilocytosis. ASCP Check Sample, Hematology No. H85-5 (H-160).

Letters to the Editor

The *Annals of Saudi Medicine* welcomes letters to the Editor from its readers. They may be on any topic, though the Editor especially encourages discussion of papers published in the *Annals*. Letters should be no more than 100 typewritten lines in length, typed double-spaced, and submitted in triplicate. Letters may include one figure or brief table and up to five references. Submission of a letter constitutes permission for the *Annals* to use it for publication, letters should not duplicate similar material being submitted or published elsewhere, and the *Annals* reserves the right to edit letters submitted. Letters referring to a recent *Annals* article should be received within 6 weeks of the article's publication.

Male Infertility

To the Editor: The study by Jamal et al [1] is very interesting because it relates to infertility data not previously reported from Saudi Arabia. Furthermore the data are compared with those from several other locations including Germany, Canada, and the United States. With very few exceptions, the percentages reported are almost identical with figures we published in 1964 [2] (Table 1).

The coincidence of polythelia (supernumerary nipples) with infertility is more than four times the

TABLE 1. Male infertility parameters.

Parameter	Haddad & Kouyoumjian [2]	Jamal et al [1]
Primary testicular failure	39%	38%
Azoospermia	34%	27%
Idiopathic infertility	25%	23%
Positive sex chromatin	16% [3]	
Cryptorchidism	11%	6%
Diabetes	10%	12%
Varicocele	9%	7%
Premature graying of the hair	8%	
Iatrogenic infertility (previous surgery)	5%	
Polythelia	4.7%	
History of mumps	2.4%	5%
Congenital anomalies of the vas	1.6%	2%
Radiation	1.6%	
Typhoid fever	0.8%	

chance of their random coincidence and is therefore a significant finding. In one of our patients a quasi-polythelia was found where only a tuft of hair was found at the expected location of the supernumerary nipple; we termed this "forme fruste polytrichelia" [2,3].

Among the vas anomalies, we described one which had not been described before: "congenital intercalation or transportation of the epididymis between two segments of vas deferens associated with an azoospermic abdominal testicle" [3].

The recent genetic engineering work on retinoblastoma cells has resulted in a reduction of tumorigenicity [3]. The translation of this experimental work into clinical practice cannot be very far off. In view of the future possibility of treating a group of infertile males by genetic engineering, the study of the genetic basis of male infertility acquires a distinct priority. It has been found recently that the incidence of chromosome anomalies in primary male sterility is of the order of 7%; it rises with a fall of sperm to reach a maximum of 25% in azoospermia. These anomalies involve the sex chromosomes (XXY, XX, XYY, Yq del, 45X) four times more frequently than the somatic chromosomes where various translocations occur in chromosomes 2,4,6-9,12-14,17,18,21,22,25 and 32 [3]. A case of oligospermia with a double orchidoma has been reported recently with an abnormal chromosome i(12p); the patient's brother also had a double orchidoma [4].

I would mention that the rebound phenomenon that occurs after the use of testosterone was first described in 1951 by Heckel [5] and not in 1972 by Rowley and Heller.

Farid Sami Haddad, BA, MD, FACS, DABU
Urology Section
Carl T. Hayden Veterans
Administration Medical Center
Phoenix, Arizona 85012
U.S.A.

References

1. Jamal A, Aboumelha MS, El-Otaibi K. Male infertility: 155 consecutive cases. *Ann Saudi Med* 1990;10(1):45-50.
2. Haddad FS, Kouyoumjian A. Clinical aspects of male sterility-pathology and classification of 123 cases. *Leb Med J* 1964;17:43-59.

3. Haddad FS, Khoury F. Chromosome anomalies in male infertility (in press).
4. Haddad FS, Sorini PM, Somsin AA, et al. Germ cell tumors of the testicle or "orchidomata". *Urol Intern* 1989;44:20-4.
5. Heckel NJ, McDonald JH. The rebound phenomenon of the spermatogenic activity of the human testis following the administration of testosterone propionate. *Fert & Steril* 1951;3(1):49-56.

Guar Gum In Non-Insulin Dependent Diabetes Mellitus

To the Editor: We read with interest the paper of Mohammed A. Laajam, et al [1] on "Guar gum in non-insulin dependent diabetes mellitus". We want to share our experience [2,3] with guar gum in diabetic subjects in India, both insulin dependent (IDDM) and non-insulin dependent (NIDDM).

We studied the effect of guar gum in 10 IDDM (8 males and 2 females, BMI = 22.77 ± 4.43) and 14 NIDDM (10 males and 4 females, BMI = 23.41 ± 2.73) as a single blind cross over study for two months.

We emphasized that we used guar gum granules in the dose of 5 grams per day only. The patients were asked to take 5 gram granules with 200 ml water before lunch. The diet of the patients was composed of 60% carbohydrates, 20% proteins and 20% fats (10% polyunsaturated fatty acids + 10% saturated fatty acids) and 20-25 grams fiber per day.

We found a statistically significant reduction in overall glycemic response (from fasting to 2 hours post glucose blood sugar values) ($P = < 0.001$) and in glycosylated hemoglobin ($P = < 0.001$) after two months of guar diet (Table 1).

The most curious aspect observed in the study is the decreased insulin requirement in IDDM and increased serum c-peptide secretion in both types of diabetics (Table 1) after guar diet.

We have also observed flatulence, dyspepsia and altered bowel habit initially, but with regular use for 1-2 weeks, these side effects decreased. All patients found guar gum palatable.

Our study concluded that guar gum in low doses can be beneficial as an adjunct to a high carbohydrate diet in both types of diabetics.

There is need for further study of the long term and sustained effects of low doses of guar gum.

Arvind Gupta, MD

Consultant Physician

Department of Medicine

E.S.I. Hospital, Jaipur, India

References

1. Laajam MA, Jim LK, El-Bolbol S, et al. Guar gum in non-insulin dependent diabetes mellitus. A double blind crossover placebo controlled trial in Saudi Arabian patients. *Ann Saudi Med* 1990;10(5):525-30.
2. Gupta A, Singh V. Study of effect of guar gum on long term glycaemic control in patients of diabetes mellitus. *J Assoc Physicians India* 1988;35:204-6.
3. Gupta A, Singh V, Sangal BC. Analysis of B-cells function and lipid profile after guar gum therapy in insulin dependent (IDDM) and non insulin dependent diabetes mellitus (NIDDM). (Unpublished data).

Concomitant Lymphoma and Carcinoma

To the Editor: Gastroscopy was performed on a 66-year-old man because of a nine month history of epigastric pain and weight loss (20 kg). Gastroscopy revealed a polypoid stomach tumor involv-

TABLE 1: Summary of AUC of blood glucose, glycosylated hemoglobin, serum C-peptide and dose of insulin in diabetic patients.

	AUC of blood glucose		Hb A1 (%)		C-peptide (ng/ml)		Dose of insulin (IU/day)	
	Before	After	Before	After	Before	After	Before	After
IDDM	654.9	498.59	7.7	6.25	1.48	1.94	36.2	24.3
(N = 10)	± 155.8	± 96.89	± 0.45	± 0.67	± 0.23	± 0.22	± 19.38	± 13.10
P		< 0.001		< 0.001		< 0.001		< 0.01
NIDDM	539.34	421.68	6.58	5.78	2.00	2.47		
(N = 14)	± 158.13	± 99.68	± 0.72	± 0.90	± 0.27	± 0.33		
P		≤ 0.001		< 0.001		< 0.001		

IDDM = insulin dependent diabetes mellitus; NIDDM = non-insulin-dependent diabetes mellitus; AUC = area under concentration curve; Hb A1 = glycosylated hemoglobin.

ing the whole lesser curvature and extending into the cardia. Gastric biopsies were taken which showed adenocarcinoma.

Clinical examination showed a healthy looking man, weighing 85 kg. A right supraclavicular lymph node was enlarged (1.5 cm in diameter) as well as axillary and inguinal lymph nodes. The spleen was slightly enlarged.

Full blood count (CBC), urea and electrolytes, liver function tests, urine analysis, chest x-ray, and barium enema were all normal.

Abdominal CT scan showed the presence of a gastric lesion with enlarged para-aortic and iliac lymph nodes. Supraclavicular lymph node biopsy revealed non-Hodgkin's lymphoma of the large cell immunoblastic type (Kiel classification). Bone marrow aspiration showed marrow infiltration by malignant lymphoma.

At operation, a huge stomach mass was present which involved the lesser curvature and posterior wall of the stomach. The para-aortic and mesen-

teric lymph nodes were enlarged and intra-peritoneal spread was present. Total gastrectomy, splenectomy, greater omentectomy, esophagojejunostomy and jejunostomy by Roux-en-Y anastomosis were performed. A wedge liver biopsy was also taken.

The gastrectomy specimen showed a huge ulcerating growth on the lesser curvature measuring 6.5×3.5 cm, approaching the esophagogastric junction and invading the entire gastric wall thickness. The lesser curvature lymph nodes were enlarged forming a mass $6 \times 5.5 \times 4$ cm. The omentum contained lymph nodes infiltrated by tumor. The spleen was enlarged weighing 340 gm and the cut surface revealed pale tumor deposits. The stomach was infiltrated by adenocarcinoma which extended to the serosa. In addition, the mucosa contained numerous lymphomatous deposits. The lesser curvature lymph nodes and omentum contained both malignant lymphoma and metastatic adenocarcinoma (Figure 1).

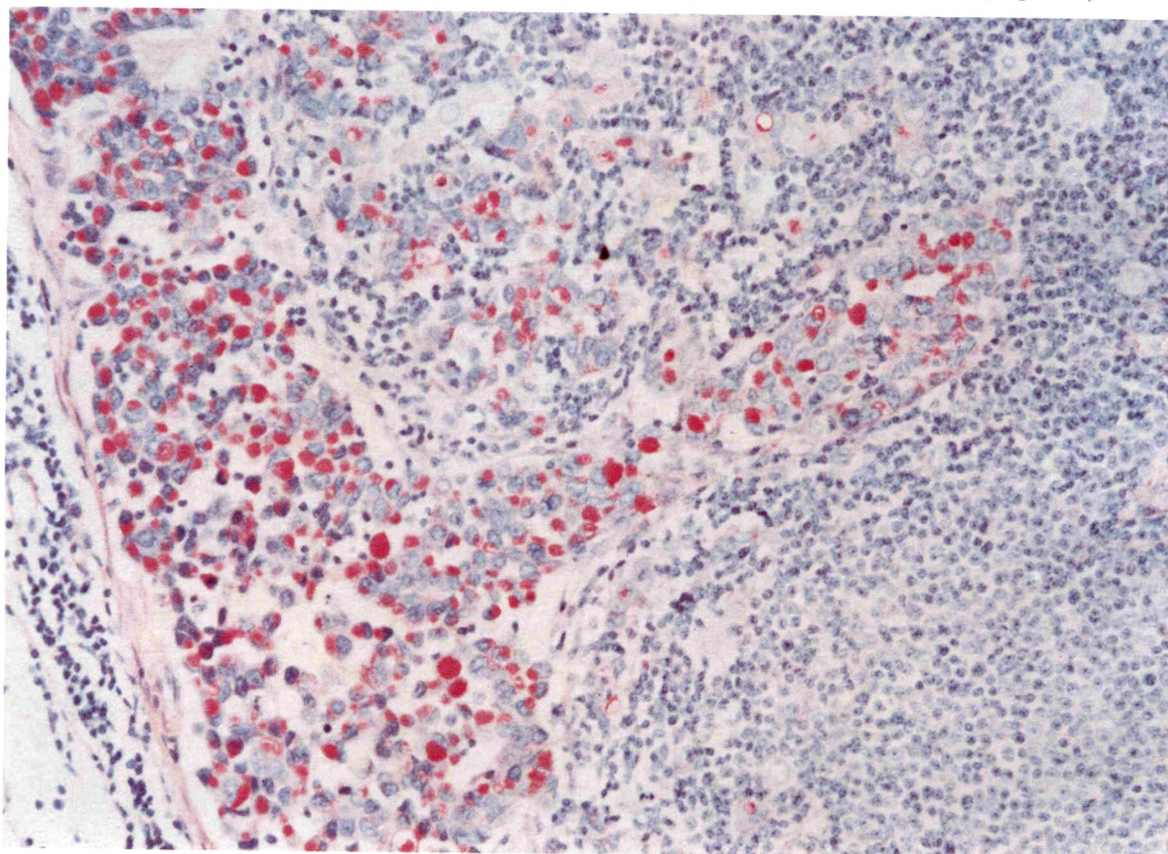


FIGURE 1. Subcapsular sinus of lymph node infiltrated by adenocarcinoma showing signet ring cells. (Periodic acid-Schiff; original magnification $\times 100$.)

Malignant lymphoma and adenocarcinoma (Figure 2) were also present in the liver biopsy which also contained a schistosoma ovum granuloma. The lymphomatous infiltrates were diffuse and consisted of a mixture of small and large cells.

Adenocarcinoma is the commonest tumor of the stomach and synchronous carcinomas occurred in 1.25% of cases [1,2]. While gastric involvement by Hodgkin's disease remains rare, there has been an increase in non-Hodgkin's gastric lymphoma [3].

Rarely malignant lymphoma and adenocarcinoma (collision tumors) have been reported [4,5]. Collision tumors have been defined as two primary histologically different malignancies developing in the same organ in close contact with little intermingling. Less than 40 cases have been reported, with most collision tumors found between the fifth and seventh decades, being

about six times more common in males. Causal relationship in synchronous development of these collision tumors is uncertain. Possibly the two tumors arise independently under the influence of the same carcinogenic action or that one tumor may produce the other.

Cornes [6] reported six cases of malignant lymphoma and adenocarcinoma of the gastrointestinal tract, noting that the relationship between them is uncertain.

Collision tumors of the gastrointestinal tract are usually malignant lymphoma and adenocarcinoma with malignant lymphoma usually predominating at the time of diagnosis [1]. Thus, our case is unusual in that both tumors occurred simultaneously.

The coexistence of two malignant tumors ("collision tumors") in one organ presents an interesting histological and clinical entity, with less than 40 cases having been reported in the literature.

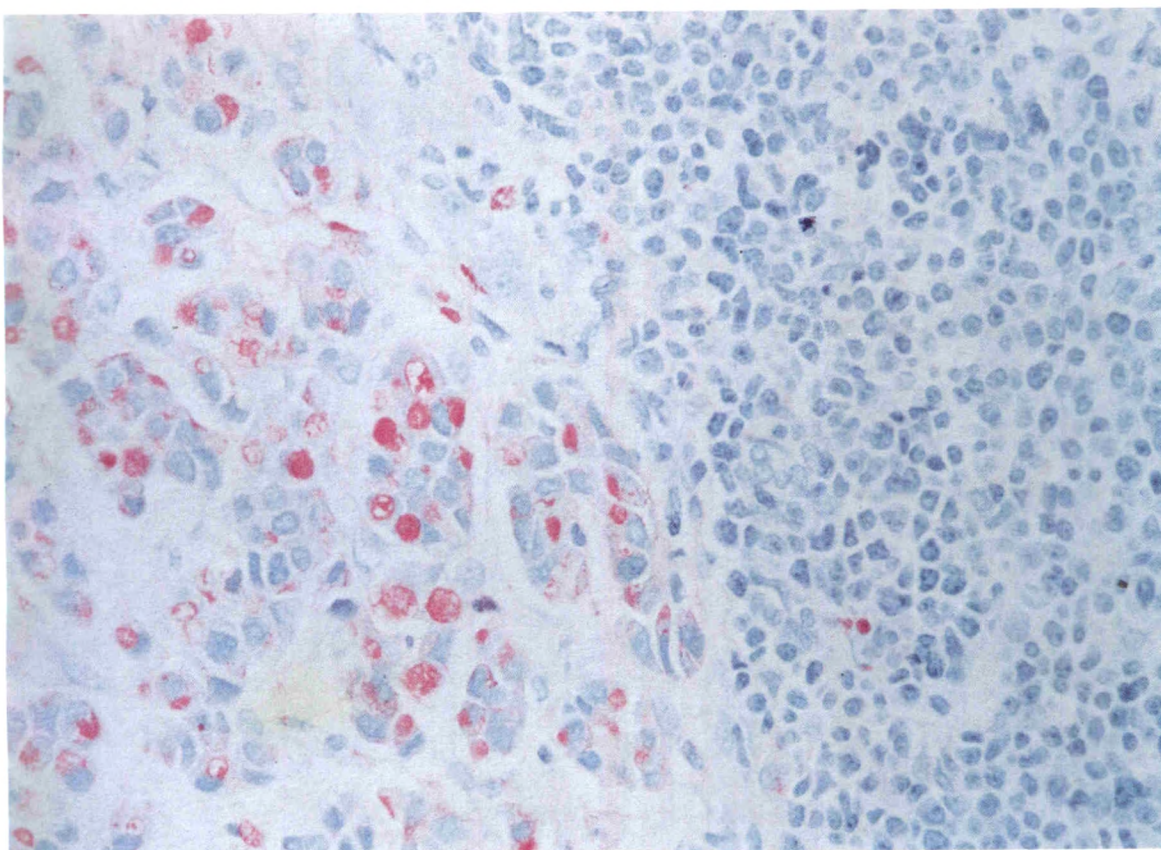


FIGURE 2. Adenocarcinoma with PAS-positive diastase resistant mucin adjacent to malignant lymphoma involving the liver. (Periodic acid-Schiff; original magnification $\times 200$.)

Mohamed I. Yasawy, MD, DTM
Abdel Rahman El-Shiekh Mohammed FRCP,
DTM&H, DipVen
Mohamed Ali Al-Karawi, Facharzt(W. Germany)
 Department of Gastroenterology
Kamla H. Sidky, MBCHB
 Department of Pathology
Muffak Jawdat, Facharzt
 Department of Surgery
 Riyadh Armed Forces Hospital
 P.O. Box 7897
 Riyadh 11159, Saudi Arabia

References

1. Planker M, Fischer JTH, Peter U, Borchard F. Synchronous double malignant lymphoma. Hepato-gastroenterology 1984;31:144-8.
2. Moertel CG, Barga JA, Soule EH. Multiple gastric cancers: review of the literature and study of 42 cases. Gastroenterology 1973;32:961-8.
3. Kile TS, Goldstein F. Malignant lymphoma involving the stomach. Cancer 1973;32:961-8.
4. Jernstrum P, Murray CG. Synchronous double primary lymphosarcoma and adenocarcinoma (collision tumor) of the stomach with cancer to cancer metastasis. Cancer 1966;19:60-6.
5. Rabinovitch J, Peres B, Grayze D. Co-existing lymphosarcoma and ulcerating carcinoma of the stomach. Arch Surg 1952;64:185-91.
6. Cornes JS. Multiple primary cancers: malignant lymphomas and carcinoma of intestinal tract in the same patient. J Clin Pathol 1960;13:483-9.

Management of Pyogenic Liver Abscess in Neonates

To the Editor: A 35-day-old Saudi boy developed respiratory distress from bilateral pneumonitis due to meconium aspiration. He required ventilation for 8 days, and an umbilical vein catheterization for 2 days. He had thrombocytopenia of $16 \times 103/\text{cmm}$. Leukocytosis of $32 \times 103/\text{cmm}$ and Hgb of $15.3 \times \text{g/L}$. Two days later he developed fresh signs of sepsis with hepatosplenomegaly, abdominal distension, and generalized erythematous rash. At this stage he had Hgb 15.3 g/L , WBC $45 \times 103/\text{cmm}$ and platelet count of 32×103 ; liver enzymes were within normal limits, and PT and PTT were prolonged $> 100 \text{ sec}$. Culture of blood, cerebrospinal fluid, and urine were sterile; but that of umbilical venous catheter tip grew *Staph epidermidis* sensitive to cephalothin, cloxacillin and cefatoxin. The boy was started on cefatoxin.

Because of the continuing signs of sepsis, an ultrasound and CT scan of the abdomen were done. The results showed a lesion measuring 2.5 cm consistent with a liver abscess (Figure 1). He was referred to our hospital a week later for further management of the liver abscess.

On examination the infant looked healthy, alert, and active, with no dysmorphic feature, except premature closure of coronal suture, with small anterior fontanelle. The liver was palpable 2 cm below the costal margin. The spleen was just palpable. Hgb was 13.2 g/L , WBC 16.8×103 , platelets $147 \times 103/\text{cmm}$. PT, PTT, and liver enzymes were within normal limits. A radioisotope, sonographic, and CT scanning of the abdomen revealed markedly decreased liver abscess.

Because of favorable clinical and radiological data, it was decided to continue the conservative management, using a combination of Cephalothin, Cefatoxin and Cloxacillin. Three weeks later, chest x-rays and CT scanning showed a normal lung and complete resolution of the liver abscess. Antibiotics were stopped and the boy discharged in good health, which continued to be evident when the patient was seen a month later.

Pyogenic liver abscess is rare in children, and rarer still in neonates. In an extensive review of literature, Moss and Pysher [4] found only 24 reported cases and added 13 from their institution; but the prevalence will remain unknown, because autopsies are not done routinely, and many cases will escape diagnosis.

The diagnosis is often missed, or delayed, because of the absence of specific signs or symptoms; these are usually the result of sepsis



FIGURE 1. CT scan showing a liver abscess of about 2.5 cm in diameter.

[3,4]. Out of 13 reported cases, only one was recognized before death [4]. The delay of diagnosis in our case, despite the presence of many risk factors, such as umbilical vein catheter [5], asphyxia neonatorum and sepsis, was due to the absence of specific signs and symptoms. Moreover, the presence of aspiration pneumonitis overshadowed the true lesion. Fever, as a symptom, may not be specific of hepatic lesion. This is particularly true in the neonates reported by Moss and Pysher [4], where only 3 out of thirteen neonates were significantly pyrexial. This is in contrast with other reports, where a number of children older than one month were febrile.

The peripheral blood picture shows a wide variation in leukocyte and platelet counts [3,4], and the liver enzymes are inconsistent. Therefore the need for a high index of suspicion is necessary.

Traditionally the treatment is surgical drainage. However, there are recent reports of a small series of patients, mostly adults, in whom non-surgical management has been successful [2]. A similar approach has been adopted on individual infants [3]. Our own experience with the reported infant is that the condition is amenable to intensive medical treatment, including serial monitoring of the abscess cavity by CT scanning.

The reported microorganisms responsible for liver infection in children are staphylococcus aureus, gram negative, and anaerobic organisms [3,4]. The choice of antibiotic, therefore, must be a broad-spectrum coverage, which can be used over a number of days without serious side-effects.

Our patient was the fifth infant, so far, reported successfully treated non-surgically.

A. Latif Al-Arfaj, MD

Thogbah, P.O. Box 20325

Al-Khobar 31952, Saudi Arabia

References

1. Tam PKH, Saing H, Lau JTK. Three successfully treated cases of nonamoebic liver abscess. *Arch Dis Child* 1983;58:828-9.
2. Herbert DA, Fogel DA, Rothman J, et al. Pyogenic liver abscesses: successful non-surgical therapy. *Lancet* 1982;1:134-6.
3. Karrar ZA, Abdullah MA. Pyogenic liver abscess in children: a report of three patients and review of the literature. *Ann Trop Paediatr* 1985;5:97-101.
4. Moss TJ, Pysher. Hepatic abscess in neonates. *Am J Dis Child* 1981;135:726-8.
5. Fraga JR, Javate BA, Vekateson S. Liver abscess and sepsis due to *Klebsiella pneumoniae* in a newborn: a complication of umbilical vein catheterization. *Clin Paediatr* 1974;13:1081-2.

Polymorphic Acetylation of Sulphadimidine in Healthy Northern Sudanese

To the Editor: It is well known that some drugs like dapson, isoniazid, nitrazepam and sulphadimidine are polymorphically acetylated in man and that some persons are genetically constituted as slow acetylators (Mendelian recessive) and others are rapid acetylators (dominant) [1]. The determination of the acetylation phenotype has been shown to be clinically important for a number of drugs including isoniazid, sulphadimidine and procainamide. Acetylation phenotype is a determinant of susceptibility to cancer induced by aromatic amine carcinogens and to other human diseases [2].

Although the acetylation status has long been known to vary in different racial groups [3], information regarding rates of acetylation in different races is at variance. For example, McQueen states that 82% of Egyptians are slow acetylators [4], while Gram mentions that Egyptians are mostly rapid acetylators [5]. Although it has been briefly mentioned that Southern Sudanese Negroes acetylate sulphadimidine slowly [4], there seems to be no information on the acetylation phenotype of Northern Sudanese people of Arabic origin. In view of the fact that drugs like dapson, isoniazid and sulphadimidine are still commonly used in the Sudan to treat leprosy, tuberculosis and other diseases, we have investigated the acetylation phenotype of a selected population of Sudanese of Arabic origin.

Fifty healthy Sudanese volunteers aged between 24 to 38 years participated in this study. Five of the volunteers were females. None of the participants had any significant medical or surgical history. The subjects gave informed consent and were asked to abstain from taking any type of drug for two weeks before the test. The standard sulphadimidine phenotype test [6] was employed. Urine samples were collected from the subjects five hours after ingesting 1 g of sulphadimidine. Urine samples obtained were labelled with serial

numbers and analyzed for sulphadimidine and metabolites using the spectrophotometric method of Bratton and Marshall [7]. The analysis was performed blind and in duplicate. The allele frequency for the slow acetylators was determined by the Handy-Weinberg principle [8].

The frequency distribution of the rate of acetylation is shown in Figure 1. Thirty subjects (60%) had an acetylation rate of less than 70% and were considered slow acetylators. The allele frequency for slow acetylators was calculated to be 0.78 ± 0.04 (S.E.).

These Northern Sudanese volunteers are of Arabic origin. The value obtained for the slower acetylators in the present work (60%) is lower than the 82% reported for negroes of Southern Sudan [4]. Our results are also lower than those reported from the neighboring countries Libya (72%) [3] and Egypt (82%) [8], both of which are of similar latitude. The value obtained here of slow allele frequency (0.78) is higher than that found for most Caucasian groups, but is somewhat lower than the 0.90 reported by Hashem et al [8]. These differences may be due to greater ethnic homogeneity of the subjects of these studies compared with the Northern Sudanese in our study, or possibly differences in methodology of the investigation.

The determination of the acetylation phenotype for sulphadimidine can be employed

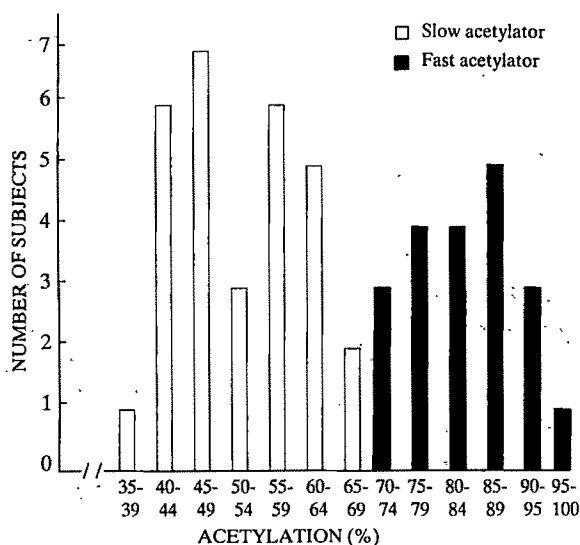


FIGURE 1. Frequency distribution of the percentage of acetylation among a sample of Northern Sudanese subjects.

for determining the acetylation rate of isoniazid [9]. This is particularly relevant to the Sudan, where isoniazid is commonly used for the treatment of tuberculosis.

In the words of Weber and Hein [2] "The acetylation status of many third world countries needs to be assessed to complete our knowledge of ethnic and geographic variation in N-acetylation capacity."

B.H. Ali, PhD

A.A. Bashir, PhD

Department of Pharmacology

Faculty of Medicine

Al-Arab Medical University

Benghazi, Libya

References

1. Evans DAP. Pharmacogenetics. *Am J Med* 1963;34:639-62.
2. Weber WW, Hein DW. N-acetylation pharmacogenetics. *Pharmacol Rev* 1985;37:25-79.
3. Karim AKMB, El-Fellah MS, Evans DAP. Human acetylation polymorphism: estimate of allele frequency in Libya and details of global distribution. *J Med Genet* 1981;18:325-30.
4. McQueen EG. Pharmacological basis of adverse drug reactions. In: Avery GS, ed. *Drug Treatment*, ed 2. 1980;221.
5. Gram TE. Metabolism of drugs. In: Craig CR, Stitzel RE, eds. *Modern Pharmacology*, ed 2. Boston: Little Brown, 1986;60.
6. Evans DAP. An improved and simplified method for detecting the acetylation phenotype. *J Med Genet* 1969;6:405-7.
7. Bratton AC, Marshall EK. A new coupling component for sulphanilamide determination. *J Biol Chem* 1939;128:537-50.
8. Emery AEH. *Methodology in Medical Genetics*. Edinburgh: Churchill and Livingstone. 1976;4-5.
9. Hashem N, Khalifa S, Nour A. The frequency of isoniazid acetylase enzyme deficiency among Egyptians. *Am J Phys Anthropol* 1969;31:97-102.
10. Rao KVN, Mitchison DA, Nair NGK, et al. Sulphadimidine acetylation test for classification of patients as slow or rapid inactivators of isoniazid. *Br Med J* 1970;3:495-7.

Spontaneous Bacterial Peritonitis Due to *Aeromonas Hydrophila*

To the Editor: Spontaneous bacterial peritonitis can occur suddenly as a complication of liver cirrhosis and ascites without any recognizable cause of focal infection. The mortality is high if this condition is not detected early, with recurrence as

high as 43% at six months, up to 60% at one year [1]. We describe here a patient who had recurrent spontaneous bacterial peritonitis, in whom the initial pathogen was *Aeromonas hydrophila*.

A 52-year-old Saudi male had suffered from chronic active hepatitis with portal hypertension for 8 years. He had several previous admissions to other Saudi hospitals for progressively increasing ascites. He was admitted to this hospital for mental confusion, fever, fatigue and increasing ascites. He denied any history of blood loss, drug abuse or alcohol consumption. On examination he looked ill and was deeply jaundiced and febrile with a temperature of 38.5°C. There was no peripheral lymphadenopathy. He showed stigmata of chronic liver disease. Examination revealed a soft tender abdomen with moderate ascites. His liver was 6 cm below the costal margin on percussion. There was no other abdominal mass. He was drowsy, irritable and confused. His outstretched hands showed hepatic flap. His deep tendon reflexes were exaggerated with equivocal plantar responses. Other systems were normal. A clinical diagnosis of hepatic encephalopathy precipitated by an infection was considered.

His full blood count showed leukocytes $9.3 \times 10^9/L$ (polymorphonucleocytes 80%), platelets $800 \times 10^9/L$ with hemoglobin 114 g/L. His erythrocyte sedimentation rate (ESR) was 30 mm/hour. He had hyponatremia (serum sodium 125 mmol/L), hypokalemia (2.4 mmol/L) with normal renal function tests. His serum bilirubin was elevated at 154 mmol/L (normal 7-17 mmol/L), raised alkaline phosphate at 312 μ/L (normal 35-125 μ/L) with normal transaminases. His serum albumin was low at 22 g/L and globulin level was raised at 42 g/L. A midstream urine was normal. His hepatitis screen was negative (HBsAG, Anti-HBc). Serum auto-antibody screen was negative. Serum alpha-fetoprotein was normal.

Abdominal ultrasound showed a contracted, hyperechogenic liver with gross ascites and multiple stones in the gallbladder. A diagnostic ascitic tap showed straw-colored exudative fluid (protein 6 g/L) with white cell count of $6 \times 10^9/L$ (80% polymorphs, 20% lymphocytes). No organisms were detected on Gram stain. Culture of both ascitic fluid and blood produced a pure growth of *Aeromonas hydrophila*.

A diagnosis of hepatic encephalopathy precipi-

tated by spontaneous bacterial peritonitis was made. He was treated with high calorie diet, restricted salt, oral lactulose, bowel washout, potassium supplement along with parenteral therapy with cefuroxime for ten days, and he recovered fully.

After discharge he was followed closely but four months later he was readmitted with another episode of hepatic encephalopathy due to recurrence of spontaneous bacterial peritonitis. On this occasion *E. coli* was isolated from the ascitic fluid.

Despite aggressive therapy the patient went into hepatorenal failure and died twelve days after admission.

Spontaneous bacterial peritonitis is defined as invasion of the peritoneum by pathogenic organisms most commonly from the gastrointestinal tract [2] without any apparent cause other than advanced chronic liver disease. The condition will be underdiagnosed if the clinician awaits the full-blown picture of peritonitis as the classical features of peritonitis may be absent. Several mechanisms have been suggested, including reduced complement level; deficiency of opsonic activity; and lack of phagocytic activity in a large volume of ascitic fluid [2].

It is important that when spontaneous bacterial peritonitis is suspected clinically, a diagnostic ascitic tap be performed and a detailed examination of the ascitic fluid carried out. The polymorphonuclear leukocyte count (PMN) is crucial; a PMN greater than 250 cells/cm is a reliable diagnostic index [3] though based on larger series, when the PMN count has been greater than 500 cells/cm, empirical therapy with antibiotics has been recommended [2].

Recurrence of this condition was thought not to be a common event, but recently Tito et al [1] expressed a contrary view. Our case is the first report from Saudi Arabia of spontaneous bacterial peritonitis by the facultative anaerobe *Aeromonas hydrophila*. The organism is a non-sporing, non-capsulated, Gram-negative motile bacillus which is catalase and oxidase positive. Full identification was obtained from the API20E system and the organism was sensitive to cefuroxime, gentamicin, amoxicillin/clavulanic acid.

Aeromonas hydrophila may be found in fresh, otherwise uncontaminated water. It may cause

colitis and diarrhea in adults but seldom causes systemic illness unless there is severe underlying disease such as cancer, leukemia, or hepatic cirrhosis. Infection of ascitic fluid may result from transmural migration from the bowel [4].

Spontaneous bacterial peritonitis due to *Aeromonas hydrophila* has been reported before [5] but we believe this is the first account from Saudi Arabia, which in our patient was followed by recurrence due to another organism.

Jamal Hossain, MRCP(UK)

Maghoub B. Ibrahim, MRCP(UK)

Department of Medicine

John D. Barrie, MD, DipPath

Department of Pathology

National Guard King Khalid Hospital

P.O. Box 9515

Jeddah 21423, Saudi Arabia

References

1. Tito L, Rimola A, Ginis T. Recurrence of spontaneous bacterial peritonitis in cirrhosis: frequency and predictive factors. *Hepatology* 1988;8(1):27-31.
2. Hallak A. Spontaneous bacterial peritonitis. *Am J Gastroenterology* 1989;84(4):345-50.
3. Runyon BA. Spontaneous bacterial peritonitis: an explosion of information. *Hepatology* 1988;8(1):171-5.
4. Gitlin N. Spontaneous bacterial peritonitis: a current opinion in gastroenterology. 1989;5(3):358-61.
5. Bercoff E, Esperu H, et al. Peritonitis spontanée à *aeromonas hydrophila* chez le cirrhotique. A propos de 2 cas. *Revue de Médecine Interne* 1985;6(1):62-4.

Announcements

The *Annals of Saudi Medicine* is pleased to publish announcements of educational opportunities of interest to its readers. For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least 6 months before the date of occurrence. Please send relevant information to the *Annals of Saudi Medicine*, Publications Office, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

King Saud University Fellowship in Pathology

King Saud University announces the inception of a 5-year joint fellowship training program in pathology. The training will be at King Khalid University Hospital, King Faisal Specialist Hospital and Research Centre, and Riyadh Armed Forces Hospital, and is a full-time program. Application is open to interested and suitably qualified residents from all over the Kingdom. To be eligible, applicants will meet the following criteria:

1. Doctors who hold MB,BS from King Saud University or equivalent degree with at least Good grade.
2. Doctors who have finished their internship in a recognized hospital with at least a Very Good grade.
3. Successful completion of a selection examination and personal interview.
4. Applicants from other institutions should submit a letter from his/her employer that he/she will be sponsored during the whole period of training.

Applications and inquiries should be sent to the Director, Postgraduate Medical Education, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

King Faisal Specialist Hospital and Research Centre Postgraduate Training Programs

King Faisal Specialist Hospital and Research Centre is pleased to invite applications for the following full-time postgraduate training programs:

1. Arab Board residency training in the specialties of internal medicine, obstetrics/gynecology, pediatrics, and surgery.
2. Five-year pathology residency training program, affiliated with the Royal College of Pathologists of Australasia and the King Saud University.
3. Fellowships, both adult and pediatric, in cardiology, endocrinology, gastroenterology, infectious diseases, nephrology, hematology, and oncology. Also, adult pulmonary and critical care medicine, adult rheumatology, pediatric allergy and clinical immunology, neonatal/perinatal medicine, and pediatric neurology.

For further information contact the Director, Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 1837.

Radiopharmaceuticals from King Faisal Specialist Hospital and Research Centre

King Faisal Specialist Hospital and Research Centre manufactures various radiopharmaceuticals at its Radionuclide and Cyclotron Operations facility with the aid of model CS-30 Cyclotron. These radiopharmaceuticals are produced according to international standards of good manufacturing practice. The Research Centre meets the high standards of quality assurance and environmental safety with regard to radiopharmaceuticals.

Radiopharmaceuticals currently produced and available for distribution throughout the Kingdom and to adjoining Arab states are as follows: thallous (Tl-201) chloride injection ($T^{1/2} = 73$ h); gallium (Ga-67) citrate injection ($T^{1/2} = 78.3$ h); iodine-123 capsules ($T^{1/2} = 13.1$ h); iodine-123 oral solution ($T^{1/2} = 13.1$ h); iodine-123 orthiodohippurate solution ($T^{1/2} = 13.1$ h); rubidium (Rb-81) $\rightarrow$ krypton (Kr-81 m) generator ($T^{1/2} = 4.58$ h - 13 s); indium (In-111) oxine ($T^{1/2} = 67.92$ h) for cell labeling; indium (In-111) DTPA for cisternography ($T^{1/2} = 67.92$ h).

Suggestions from the medical community for additional cyclotron-produced needs are welcome.

Inquiries concerning the availability, price schedule, and technical information on specific radiopharmaceuticals should be directed to: Abbass H. Al-Marzouky, MD, Executive Director, Research Centre, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia (Fax No. 966-1-441-4839).

King Faisal Specialist Hospital and Research Centre Symposia: Educational Activities

King Faisal Specialist Hospital and Research Centre is pleased to announce the following educational activities for 1411.

1. FMGEMS Examination; 12-13 Muharram 1412 (23-24 July 1991)

For further information, contact Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211; telephone 464-7272, extension 1865 or 1834, fax 442-7237.

Fellowship and Diploma Programs, College of Medicine, King Saud University

The Postgraduate Centre for Medical Education, College of Medicine, King Saud University, announces the schedule of new intakes for the following diploma and fellowship programs for the year 1412:

Diploma in Dermatology: Selection examination (written): 7 Rabi Al Awal 1412 (15 September 1991); interview: 10 Rabi Al Awal 1412 (18 September 1991); starting date of acceptance of applications: 16 Ramadan 1411 (1 April 1991); deadline for submission: 23 Muharram 1412 (3 August 1991).

Fellowship Programme in Anaesthesia: Selection examination and interview: 28 Safar 1412 (7 September 1991); starting date of acceptance of application: 16 Ramadan 1411 (1 April 1991); closing date: 16 Muharram 1412 (27 July 1991). Application forms, list of requirements, and further informa-

tion can be obtained from the Residency Training Programme Secretary, Postgraduate Centre, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, or please call 467-1551, 467-1556, or 467-1564.

King Faisal Specialist Hospital and Research Centre Symposia: Educational Activities

King Faisal Specialist Hospital and Research Centre is pleased to announce the following educational activities for 1411.

1. FMGEMS Examination; 12-13 Muharram 1412 (23-24 July 1991)

For further information, contact Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211; telephone 464-7272, extension 1865 or 1834, fax 442-7237.

Fellowship and Diploma Programs, College of Medicine, King Saud University

The Postgraduate Centre for Medical Education, College of Medicine, King Saud University, announces the schedule of new intakes for the following diploma and fellowship programs for the year 1412:

Diploma in Dermatology: Selection examination (written): 7 Rabi Al Awal 1412 (15 September 1991); interview: 10 Rabi Al Awal 1412 (18 September 1991); starting date of acceptance of applications: 16 Ramadan 1411 (1 April 1991); deadline for submission: 23 Muharram 1412 (3 August 1991).

Fellowship Programme in Anaesthesia: Selection examination and interview: 28 Safar 1412 (7 September 1991); starting date of acceptance of application: 16 Ramadan 1411 (1 April 1991); closing date: 16 Muharram 1412 (27 July 1991). Application forms, list of requirements, and further information can be obtained from the Residency Training Programme Secretary, Postgraduate Centre, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, or please call 467-1551, 467-1556, or 467-1564.

Chinese University of Hong Kong, Fourth International Imaging Course

The Fourth International Imaging Course (35 hours of Category I accreditation) will be held from 30 September to 5 October, 1991, at the Regal Riverside Hotel, Hong Kong. Course Organizers are: Professors L. Kreel, C. Metreweli, and T.L. Lawson. For further information, please contact: Miss Rebecca Tsui, Department of Radiology, Prince of Wales Hospital, Shatin, Hong Kong. Tel: (852) 636 3213; Fax: (852) 636 0012.

Molecular Aspects of Autoimmunity

A Satellite meeting of the VIII International Congress of Immunology will be held in Mainz, Germany, August 18th-22nd 1992. This 2½-day meeting will feature plenary lectures, posters, and round table discussions on: antigen processing and presentation, major histocompatibility complex structure and function, T-cell receptor usage, second signal, transgenic mouse models, and clinical immunology.

Registration will be limited to 350 persons. Those interested in presenting posters or who require further information should contact: Nadir R. Farid, Chairman, Organizing Committee, Molecular Aspects of Autoimmunity, Department of Medicine, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Kingdom of Saudi Arabia.

Medical Oncology Fellowship, King Faisal Specialist Hospital and Research Centre

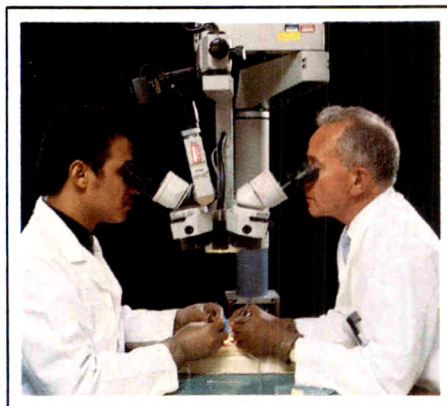
Medical Oncology Fellowships are being offered by the Section of Medical Oncology, Department of Oncology, King Faisal Specialist Hospital and Research Centre. The two-year fellowship program will provide successful candidates with comprehensive clinical and basic Medical Oncology experience. Major emphasis is placed on standard and experimental clinical protocols with systemic chemotherapy and immunotherapy for solid tumors. Fellows will also be involved in educational activities of the Department. Prospective applicants must have successfully completed training in an accredited medical residency training programme and passed the Arab Board's certifying examination or its equivalent. At the end of the Fellowship after successful examinations, Fellows will be awarded a Certificate of competence in the Subspeciality in Medical Oncology and an optional third year in the field of basic or clinical oncology of their choice will be offered to selected candidates based on career objectives.

Candidates should send their application, C.V., and names of three referees to Director, Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211; Fax 442-7237.

Correction

In the article by Iyengar et al, "Tracheoesophageal fistula, esophageal atresia, and left pulmonary agenesis" (1991;11:228-9), Figures 1 and 2 have been reversed. Figure 1, as it was published, is Figure 2 and vice versa. The legends are correct. Please note this in your copies of the March 1991 issue of the *Annals*.

**KING FAISAL SPECIALIST HOSPITAL
AND
RESEARCH CENTRE**



Invites Applicants for the Following Fellowship Programs

Cardiovascular Diseases

Cardiology
Pediatric Cardiology
Thoracic Cardiovascular Surgery

Oncology

Hematology
Medical Oncology
Pediatric Hematology-Oncology

Medicine

Endocrinology
Gastroenterology
Infectious Diseases
Nephrology
Rheumatology

Pediatrics

Allergy and Clinical Immunology
Neonatal/Perinatal Medicine
Genetics, Metabolic Diseases,
and Endocrinology
Infectious Diseases
Nephrology
Neurology

Neurosciences

Neurosurgery

We are a major tertiary care centre providing a unique environment to train subspecialists. There are patients with unusual clinical entities, highly qualified staff, state-of-the-art equipment, and a total commitment by Administration to train Saudi physicians to assume the role of subspecialists in the Kingdom of Saudi Arabia. Applicants must be Saudis who are Arab Board certified in their specialty (or equivalent certification).

Contact Person:

Dr. Abdullah Al-Dalaan, Deputy Director, Academic Affairs and Post Graduate Education
(MBC-36), King Faisal Specialist Hospital and Research Centre
P.O. Box 3354, Riyadh 11211, Saudi Arabia
Telephone: 464-7272 Ext. 1832 or Fax: 442-7237

المدونات الطبية السعودية

هيئة التحرير

رئيس التحرير الدكتور محمد أخت

الدكتور عبدالعزيز المشاري
الدكتور منصور النزهة
الدكتور خالد طبارة
الدكتور سعدي طاهر

الدكتور ماجد عامر
الدكتور كارلوس دوران
الدكتور صلاح الفقيه
الدكتور نادر فريد
الدكتور محمد زهير القاوي

مساعدتنا التحرير:

فرجينيا جي كروزيير
شيرلي موفيت

هيئة النشر:

رئيس التحرير: الدكتور محمد أخت
المحرر الإداري: الدكتور سعدي طاهر
محرر النصوص العربية: الدكتور محمد زهير القاوي
مساعدة محرر فني: ماري آن دي سانتس

المدونات الطبية السعودية مجلة تنشر بموجب الأمر الملكي السامي رقم ٥/م/٢٤٢٢٣ بتاريخ ١٤ شوال عام ١٤٠٠ هـ. وتصدر مرة كل شهرين، وهي مشروع مشترك بين كل من كلية الطب ومستشفى الملك خالد الجامعي - جامعة الملك سعود، صندوق بريد ٢٩٢٥ - الرياض ١١٤٦١، المملكة العربية السعودية، ومستشفى الملك فيصل التخصصي ومركز الأبحاث، صندوق بريد ٣٣٥٤ - الرياض ١١٢١١، المملكة العربية السعودية. يتم صف وطبع المجلة بمطابع جامعة الملك سعود. يتم توزيع المدونات بواسطة قسم البريد التابع لإدارة الخدمات الإدارية بمستشفى الملك فيصل التخصصي ومركز الأبحاث. كما يتولى قسم الترجمة في هذه الإدارة إعداد الملخصات العربية بالاشتراك مع الدكتور محمد زهير القاوي. كل المراسلات والاستفسارات وطرق الحصول على المستلثات ترسل إلى مكتب المطبوعات على العنوان التالي:

مندوب الاعلانات

بائريس هاوس

بانستيد يسري

المملكة المتحدة

مكتب المطبوعات

مدونات الطب السعودي

مستشفى الملك فيصل التخصصي ومركز الأبحاث

ص. ب. ٣٣٥٤

الرياض ١١٢١١ - المملكة العربية السعودية

الآراء التي ترد في المقالات المنشورة تعبر عن رأي أصحابها فقط ولا تعبر عن وجهة نظر مجلة المدونات الطبية السعودية. لا يسمح بإعادة طبع أي جزء من المجلة أو نسخه بأي شكل وبأي وسيلة سواء أكانت إلكترونية أو آلية، بما في ذلك التصوير والتسجيل أو الإدخال في أي نظام حفظ أو استعادة معلومات إلكتروني، بدون الحصول على موافقة مسبقة من إدارة المجلة.

INFORMATION FOR AUTHORS

THE EDITORS of the *Annals of Saudi Medicine* welcome contributions from our readers. The *Annals* will consider for publication manuscripts of interest to readers in Saudi Arabia, the Middle East, and around the world. All submissions are subject to review by the Editorial Board and by referees in appropriate specialties.

Submission of Manuscripts. Manuscripts are received with the understanding that they are not under simultaneous consideration by another publication. An abstract published prior to a full report is not regarded as a duplicate publication. The author's transmittal letter must accompany the manuscript and contain these statements: "The manuscript has been seen and approved by all authors involved and is neither being published nor being considered for publication elsewhere. The authors transfer copyright to the *Annals of Saudi Medicine*." Accepted manuscripts may not be published elsewhere without *Annals'* permission.

Manuscript Preparation. The format of the *Annals of Saudi Medicine* complies with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," published by the International Committee of Medical Journal Editors in Vancouver, British Columbia, in 1979 (the widely accepted "Vancouver style"), as described in the *Annals of Internal Medicine* (1982; 96 [pt 1]: 766-71). With the exception of blood pressure, all units of measurement and laboratory values must be expressed in SI units; conventional units may be included parenthetically. Authors are referred to *Annals of Internal Medicine* (1987; 106 [1]: 114-29) for guidance in the use of SI units. Manuscripts, including tables, references, and figure legends, must be typewritten, double-spaced, on 8½ × 11 inch (21.5 × 28 cm) or size A4 paper, with margins of at least 1 inch (2.5 cm). Pages should be numbered consecutively, beginning with the title page and continuing through the last page of typewritten material. One original and two photocopies of the entire manuscript should be submitted, along with three sets of photographs.

Title Page. The title page must contain (1) title of the article, (2) correct names of each author plus highest academic degree for each, (3) each author's official academic and/or clinical title and affiliation, (4) name and address of the institution(s), (5) name and address of author to whom correspondence should be sent, if it differs from the first author, and (6) any disclaimers. For case reports, it is recommended that the number of authors be limited to four. Acknowledgment of support should be included in the Acknowledgment section at the end of the article.

Abstracts. All original articles must contain an abstract of not more than 200 words. The abstract should include statements of problem, method of study, results, and conclusions.

Manuscript Format. Most original articles have the following format: Introduction (the question the paper intends to answer); Materials and Methods (the study design and methods, definitions such as for diagnostic criteria, the population or patient samples, and laboratory and statistical methods); Results (the pertinent findings in a logical sequence with tables and figures as necessary); and Discussion (conclusions based on the findings, evidence from the literature that supports the conclusions, conflicting evidence, applicability of the conclusions, and implications for future research or clinical applications). Authors might consult recent issues of the *Annals* for examples of appropriate format.

References. List references, double-spaced, in consecutive numerical order (the order of citation in the manuscript, not alphabetically). Once a reference is cited, all subsequent citations should be to the original number. All references must be cited in the text or tables. Unpublished data and personal communications will not be accepted as references. References to journal articles should include in this order, (1) authors, (2) title, (3) journal name (as abbreviated in *Index Medicus*), (4) year, (5) volume and issue number, and (6) inclusive page numbers. References to books should include (1) authors, (2) chapter title (if any), (3) editors names (if any), (4) title of book, (5) city of publication, (6) publisher, and (7) year. Volume and edition numbers and specific page numbers should be included when appropriate. The author is responsible for the accuracy and completeness of the references and for their correct textual citation. Refer to reference citations and listings in the text for proper format.

Illustrations. Three copies of all figures or photographs should be included with the submitted manuscript. Photographs must be high-contrast, glossy, black and white prints, unmounted and untrimmed, with preferred size between 4 × 5 inches and 5 × 7 inches (10 × 13 cm and 13 × 18 cm). Color transparencies or photos will be accepted at the discretion of the Editorial Board. Figure number, name of senior author, and an arrow indicating "top" should be typed on a gummed label and affixed to the back of each illustration. Slides must be marked for "front" as well as "top." All lettering, arrows, or other artwork must be done by an artist or draftsman. Graphs and charts must also be prepared professionally by an artist or draftsman. Written permission must accompany any photograph in which the subject can be identified or any illustration that has been previously published. All illustrations ("figures") must be numbered as cited in the text in consecutive numeric order.

Legends. Captions for the figures must be typed, double-spaced, and must not appear on the figures. For photomicrographs, the legend should include the original magnification and stain used.

Tables. Each table should be typed double-spaced, including all headings. Verify tabular statistics to make sure they tally and match data cited in the text.

Responsibilities of Authors. The authors are entirely responsible for accuracy of all statements and data (including drug dosages) contained in the manuscript, accuracy of all reference information, and for obtaining and submitting permission from the author and publisher of any previously published material included in the submitted manuscript. The corresponding author will receive an edited manuscript for "final author approval." The author should review this carefully, as he is responsible for all changes in his work, including changes made by the copy editor.

Informed Consent. All manuscripts reporting the results of experimental investigation involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after approval of the experimental protocol by a local human ethics committee.

Submit manuscripts to the Publications Office, *Annals of Saudi Medicine*, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone: (01) 464-7272, extension 1817.

EMINASE

ANISTREPLASE
ANISOYLATED LYS-PLASMINOGEN STREPTOKINASE ACTIVATOR COMPLEX (APSAC)

PRESCRIBING INFORMATION



Presentation

EMINASE is supplied as a white to off-white sterile lyophilised powder in vials containing 30 Units of the p-anisoylated derivative of the primary (human) lys-plasminogen-streptokinase activator complex (APSAC; anistreplase) together with buffering and stabilising agents.

Indications

EMINASE is indicated in the treatment of acute myocardial infarction to establish reperfusion, preserve left ventricular function, limit infarct size and to reduce mortality.

Clinical studies have shown that EMINASE significantly reduces 30-day and 1-year mortality, limits infarct size and preserves left ventricular function.

Dosage and Administration

30 Units of EMINASE should be given as a single slow intravenous (IV) injection over 2-5 minutes. *Do not administer by intramuscular injection.*

EMINASE should be administered as soon as possible after the onset of symptoms of myocardial infarction.

See Package Insert Leaflet for details of preparation and administration.

Contra-Indications

Since thrombolytic therapy increases the risk of bleeding, EMINASE is contra-indicated in the following situations: 1. Surgery or major trauma within the previous 10 days. 2. Peptic ulceration, gastro-intestinal bleeding or other internal bleeding within the past 6 months. 3. Known bleeding diathesis. 4. History of cerebrovascular accident. 5. Severe, uncontrolled hypertension. 6. Known intracranial neoplasm or aneurysm. 7. Recent (within 2 months) neurosurgical procedure.

EMINASE should not be administered to patients who have experienced severe allergic reactions to this product or streptokinase.

Precautions and Warnings

Patients with any condition in which bleeding constitutes a significant hazard, or in which it would be particularly difficult to manage because of its location, should be monitored carefully. The risk associated with EMINASE therapy may be increased in such patients and should be weighed against the anticipated benefits.

Following administration of EMINASE, venepuncture and other invasive procedures should be kept to a minimum in order to reduce the risk of bleeding. In patients undergoing cardiac catheterisation, the catheter sheath should not be removed until 24 hours after dosing.

In the following conditions, the risks associated with thrombolytic therapy may be increased and should be weighed against the anticipated benefits: ● haemorrhagic diabetic retinopathy or other haemorrhagic conditions ● subacute bacterial endocarditis ● atrial or ventricular mural thrombosis, intracardiac tumours and aortic aneurysm ● septic thrombophlebitis or occluded AV cannula at a seriously infected site ● haemostatic defects including those secondary to severe hepatic or renal disease ● recent or current treatment with oral anticoagulants.

Hypotension, sometimes severe, has occasionally been observed soon after intravenous EMINASE administration. It is not recommended that EMINASE be administered rapidly (less than 2 minutes).

Re-administration

Because of the increased likelihood of resistance due to antistreptokinase antibody, EMINASE may not be effective if administered more than 5 days after prior EMINASE or streptokinase therapy, particularly between 5 days and 12 months. Furthermore, increased antistreptokinase antibodies after EMINASE or streptokinase may also increase the risk of allergic reactions following re-administration.

Elderly Patients

Experience is limited in patients over 75 years of age and the benefits of EMINASE should be balanced against risk in this group.

Adverse Events

Hypotension observed occasionally soon after EMINASE administration is usually transient and is often associated with bradycardia.

Early reactions of flushing and bradycardia (usually within the first hour) as well as fever and nausea/vomiting (usually within 6 to 24 hours) have been reported but are generally not severe.

"Allergic-type" reactions, including bronchoconstriction or anaphylaxis have been reported but are uncommon and usually transient. A purpuric rash has occasionally been reported. All cases recovered spontaneously without sequelae.

The most common complication associated with EMINASE, as with other thrombolytics, is bleeding, most frequently from arterial and venous puncture sites. Haemoptysis, haematuria, haematemesis and malaena have been reported occasionally. Cerebrovascular accidents have been reported but the incidence is low and there has usually been a predisposing factor.

Local bleeding can be controlled with pressure. In cases of severe, uncontrolled bleeding, tranexamic acid or aprotinin should be given by slow intravenous injection to stop the fibrinolytic activity of EMINASE. Additionally, cryoprecipitate, purified clotting factor concentrates or fresh whole blood may be used to correct the haemostatic deficiency. If the haematocrit has fallen significantly, a blood transfusion may be necessary.

Reperfusion-associated arrhythmias have been reported following EMINASE treatment. These are generally transient but if prolonged they can be controlled with appropriate therapy.

Availability

IV Injection Pack:

1 vial EMINASE 30 Units, a 5ml ampoule of Water for injections B.P., a 5ml disposable syringe and needle.

Storage and Stability

EMINASE should be stored in a refrigerator (2°-8°C) and must not be used after the expiry date printed on the pack and vial, EMINASE vials must not be stored at room temperature.

Further information is available on request.

EMINASE is a product of research from Beecham Pharmaceuticals, a part of SmithKline Beecham Pharmaceuticals, Brentford, England.

EMINASE and the cardiovascular logo are trade marks.

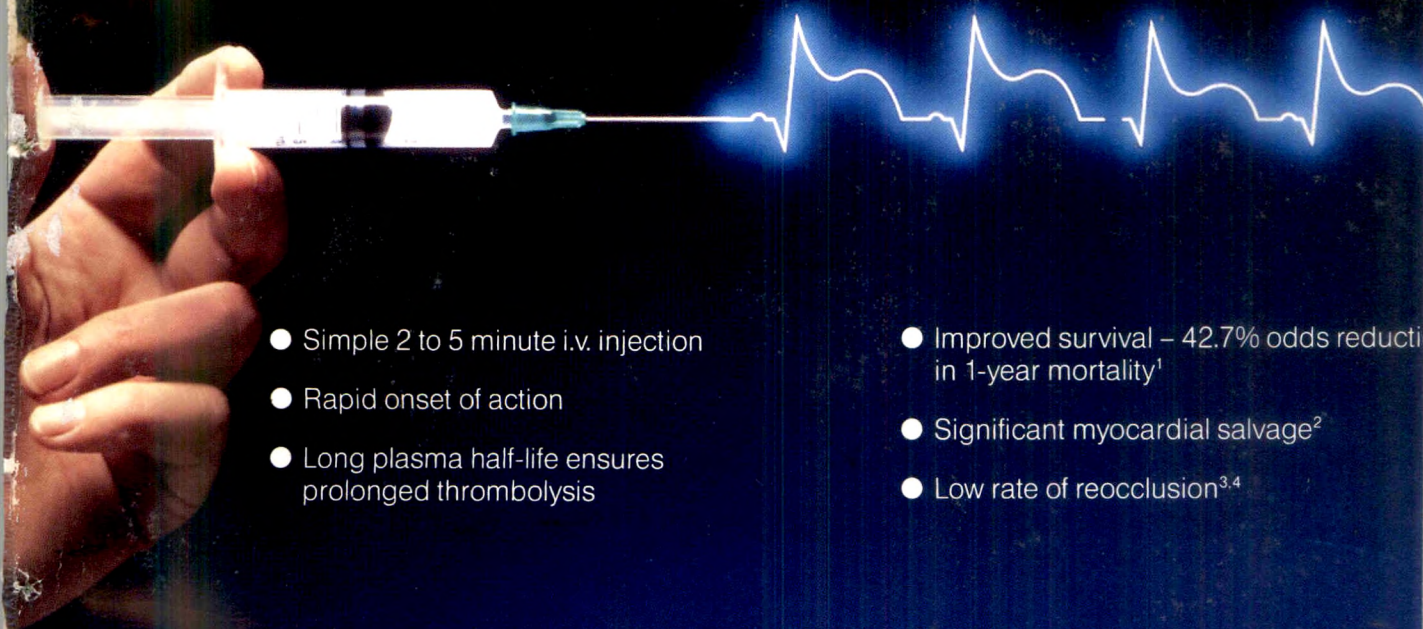
Prescribing Information revised November 1990.

488/EMI/G1/90

SB
SmithKline Beecham
Pharmaceuticals

INJECT

SURVIVE



- Simple 2 to 5 minute i.v. injection
- Rapid onset of action
- Long plasma half-life ensures prolonged thrombolysis

- Improved survival – 42.7% odds reduction in 1-year mortality¹
- Significant myocardial salvage²
- Low rate of reocclusion^{3,4}

References

1. AIMS Trial Study Group, *Lancet* 1990; **335**:427-431.
2. Bassand JP et al, *J Am Coll Cardiol* 1989; **13**:988-997.
3. Anderson JL et al, *J Am Coll Cardiol* 1988; **11**:1153-63.
4. Bonnier JJRM et al, *Am J Cardiol* 1988; **62**:25-30.

NEW

ANISTREPLASE

EMINASE

ANISOYLATED LYS-PLASMINOGEN STREPTOKINASE ACTIVATOR COMPLEX (APSAC)



simply practical thrombolysis

SB

SmithKline Beecham
Pharmaceuticals

For prescribing information see overleaf.

488/EF

ANNALS OF SAUDI MEDICINE

TABLE OF CONTENTS

Volume 11 Number 4

July 1991

EDITORIAL

Vale

Peter B. Herdson	365
------------------------	-----

ORIGINAL ARTICLES

Fine-Needle Aspiration Biopsy Diagnosis of Pediatric Neoplasms Mohammed Akhtar, M. Ashraf Ali, Anwaar Burgess, Mahmuda Huq, Mohammed Bakry	366
Fistula-In-Ano: A Pathological Study Jehoram T. Anim, Saleh A. Sawayan, Chris S. Grant, Hassan Al-Breiki	377
Jeddah Experience in the Management of High Anal Fistula Adnan Mohamed Rashid Jamjoom, Yasir Saleh Jamal	381
The Management of Anorectal Abscess: An Inexpensive and Simple Alternative Technique to Incision and "De-roofing" William H. Isbister, Stephen Kyle	385
Pancreatic Pseudocyst: A Review of 5 Years' Experience Saleh Hamza Al-Sulaimani, Mohammed Khurshid Alam	391
Damage to the Bile Ducts at Cholecystectomy Tarek Said Malatani	396
Surgical Management of Chiari Malformation and Syringomyelia: Experience in 14 Cases Naim-Ur-Rahman, Zain Alabedeen B. Jamjoom	402
The Value of Oligoclonal Bands in Neurobrucellosis Abdul Kader Daif	411
Comparative Responses of Plasma Glucose, Insulin and C-Peptide Following Ingestion of Isocaloric Glucose, a Modified Urban Saudi Breakfast and Dates in Normal Saudi Persons Mohammed Ahmed, Abdulaziz Al Othaimen, Edward De Vol, Alan Bold	414
Lipoid Proteinosis: Clinical, Genetic and Pathologic Study of a Saudi Arabian Family Mirghani A. E. Uthman, Mohamed B. Satti, Mohamed E. Baraka	418
Use of Gas Liquid Chromatography as an Adjunct to Conventional Bacteriological Methods in the Diagnosis of Anaerobic Cerebral Abscess Sabiha Pit, Farida Jamal, Fadzli K. Cheah, Mohammed Ariff Mohammed Abbas	424
Bacteriuria, Incidence, Causative Microorganism, and Susceptibility Pattern at Qatif Central Hospital Ali Magzoub El-Bashier	429
Helicobacter Pylori and Chronic Gastritis Khalid Mahmood	435
Increasing Compliance Over Five Years in a Hepatitis B Infant Immunization Program in Saudi Arabia Frank W. Kiel	439
Pulmonary Tuberculosis in Saudi Arabia: A Retrospective Study of 1566 Patients Mohammed Saleh Al-Hajjaj, Lalit Pandya, Ali A. Marie, Abdul Aziz Madani, Nasser Al-Sharif, Sulaiman Al-Majed	443
IgE-Mediated Skin Reaction Among Asthmatic Children in Riyadh Abdulrahman Al Frayh	448

SPECIAL COMMUNICATION

Nursing: Attitudes, Perceptions and Strategies for Progress in Saudi Arabia Cynthia L. Jackson, Rebecca Gary	452
---	-----

CASE REPORTS

Gluteal Necrosis with Ano-Gluteal Fistula: A Result of Umbilical Artery Catheterization A. Laif Al-Arfaj, Mohammed S. Khwaja	469
Abdominal Cocoon in a Pregnant Woman: A Case Report and Review of the Literature Kamal I. Ali Gharaibeh, N.A. Morad, E. Sunna	462
Hepatic Cystadenoma with Mesenchymal Stroma (CMS): Report of Case Presenting With Obstructive Jaundice Mohamed B. Satti, Abdulaziz A. Al-Quorain, Majed S. Al-Awami, Abdulla Y. El-Hassan, Ghassab Al-Ghassab, Abdul Aziz Al-Jamaa	465
The Budd-Chiari Syndrome: A Case Report and Review of Current Management Options Mohamed A. Al-Karawi, Abdul M. Ahmed, Abdel Rahman El-Shiekh Mohamed	471
Hereditary Pyropoikilocytosis: A Case Report with Thermal Studies and Scanning Electron Microscopy Salim H. Khalil, Randa M. Nounou	475

LETTERS TO THE EDITOR	478
-----------------------------	-----

ANNOUNCEMENTS	487
---------------------	-----

CORRECTION	488
------------------	-----